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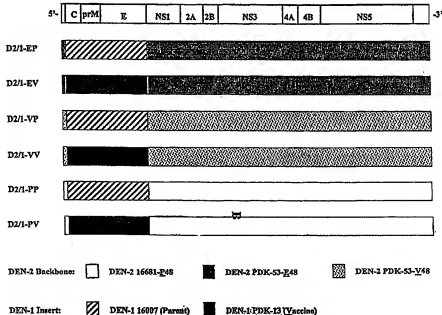
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(54) Title: **AVIRULENT, IMMUNOGENIC FLAVIVIRUS CHIMERAS**



(57) Abstract: Chimeric flaviviruses that are avirulent and immunogenic are provided. The chimeric viruses are constructed to contain amino acid mutations in the nonstructural proteins of a flavivirus. Chimeric viruses containing the attenuation-mutated nonstructural genes of the virus are used as a backbone into which the structural protein genes of a second flavivirus strain are inserted. These chimeric viruses elicit pronounced immunogenicity yet lack the accompanying clinical symptoms of viral disease. The attenuated chimeric viruses are effective as immunogens or vaccines and may be combined in a pharmaceutical composition to confer simultaneous immunity against several strains of pathogenic flaviviruses.



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AVIRULENT, IMMUNOGENIC FLAVIVIRUS CHIMERAS

This application claims priority to provisional application Serial No. 60/182,829, filed February 16, 2000, which is herein incorporated in its entirety.

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This invention was made by the Centers for Disease Control and Prevention, an agency of the United States Government. Therefore, the United States Government has certain rights in this invention.

10 **FIELD OF THE INVENTION**

The present invention relates to the fields of immunology and virology and more particularly to avirulent, immunogenic flavivirus chimeras for the production of immunogenic, live, attenuated flavivirus vaccines.

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BACKGROUND OF THE INVENTION

Dengue viruses are mosquito-borne pathogens of the genus *Flavivirus* (family Flaviviridae). Four serotypes of dengue virus (often abbreviated "DEN") have been identified, including dengue-1, dengue-2, dengue-3 and dengue-4 (DEN-1 to DEN-4). The flavivirus genome is a single-stranded, positive-sense RNA approximately 11 kb in length, containing a 5'-noncoding region (5'NC); a coding region encoding the viral structural proteins; five nonstructural proteins, designated NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5; and a 3'-noncoding region (3'NC). The viral structural proteins include the capsid, premembrane/membrane and envelope. The structural and nonstructural proteins are translated as a single polyprotein. The polyprotein is then processed by cellular and viral proteases.

Transmitted by *Aedes aegypti* mosquitoes to humans in tropical and subtropical regions of the world, dengue viruses cause millions of cases of disease every year,

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ranging from dengue fever to the often fatal dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). Secondary infection of humans with a heterologous serotype of DEN virus may induce an immunopathological response and is considered a possible risk factor for DHF/DSS. Therefore, the need exists for development of a vaccine that
5 confers simultaneous protection against all dengue virus strains.

Since eradication of *Aedes aegypti* mosquitoes appears to be practically infeasible, development of safe, effective vaccines against all four serotypes of dengue virus is a World Health Organization priority. However, no approved, effective vaccine
10 against any of the dengue virus strains is currently available. It has been demonstrated that serial passage of wild-type flaviviruses in various cell cultures, such as primary dog kidney (PDK) cells, produces virus variants that have reduced virulence, retain immunogenicity and produce no untoward clinical symptoms.

15 Live, attenuated dengue viruses of all four serotypes have been developed at Mahidol University in Thailand by passaging the wild-type viruses in cell culture. These are currently the most promising live, attenuated vaccine candidates for immunization against dengue virus infection and/or disease. These vaccine candidates have been designated by a combination of their dengue serotype, the cell line through
20 which they were passaged and the number of times they were passaged. Thus, a dengue serotype 1 wild-type virus passaged in PDK cells 13 times is designated as DEN-1 PDK-13 virus(nucleotide sequence, SEQ ID NO:3; amino acid sequence, SEQ ID NO:4). The other vaccine candidates are DEN-2 PDK-53 (nucleotide sequence, SEQ ID NO:15; amino acid sequence, SEQ ID NO:16), DEN-3 PGMK-30/FRhL-3
25 (thirty passages in primary green monkey kidney cells, followed by three passages in fetal rhesus lung cells)(nucleotide sequence, SEQ ID NO:21; amino acid sequence, SEQ ID NO:22) and DEN-4 PDK-48 (nucleotide sequence, SEQ ID NO:25; amino acid sequence, SEQ ID NO:26). These four candidate vaccine viruses were derived by tissue culture passage of wild-type parental DEN-1 16007 (nucleotide sequence, SEQ
30 ID NO:1; amino acid sequence, SEQ ID NO:2), DEN-2 16681(nucleotide sequence,

SEQ ID NO:13; amino acid sequence, SEQ ID NO:14), DEN-3 16562 (nucleotide sequence, SEQ ID NO:19; amino acid sequence, SEQ ID NO:20) and DEN-4 1036 (nucleotide sequence, SEQ ID NO:23; amino acid sequence, SEQ ID NO:24) viruses, respectively.

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Preliminary human clinical trials with these attenuated viruses have indicated that DEN-2 PDK-53 has the lowest infectious dose (50% minimal infectious dose of 5 plaque forming units or PFU) in humans, is strongly immunogenic, and produces no unacceptable clinical symptoms. The DEN-1 PDK-13, DEN-3 PGMK-30/FRhL-3 and
10 DEN-4 PDK-48 vaccine virus candidates have higher 50% minimal infectious doses of 10,000, 3500, and 150 PFU, respectively, in humans. The higher infectious doses required for the latter three vaccine candidates raises concerns regarding the relative efficacy of each serotype component in a tetravalent dengue virus vaccine. Although only one immunization with monovalent DEN-2 PDK-53 virus or DEN-4 PDK-48
15 virus was required to achieve 100% seroconversion in human subjects, a booster was needed to achieve the same seroconversion rate for DEN-1 PDK-13 and DEN-3 PGMK-30/FRhL-3 viruses, which have the two highest infectious doses for humans.

The DEN-2 PDK-53 virus vaccine candidate, henceforth abbreviated PDK-53,
20 has several measurable biological markers associated with attenuation, including temperature sensitivity, small plaque size, decreased replication in mosquito C6/36 cell culture, decreased replication in intact mosquitoes, loss of neurovirulence for suckling mice and decreased incidence of viremia in monkeys. Clinical trials of the candidate PDK-53 vaccine have demonstrated its safety and immunogenicity in humans.
25 Furthermore, the PDK-53 vaccine induces dengue virus-specific T-cell memory responses in human vaccine recipients.

Except for DEN-2 PDK-53 virus, the number and identity of the genetic mutations that accrued during multiple passages in cell culture and that are associated
30 with the attenuated phenotypes of the vaccine candidates are unknown. Neither the

relative contributions of such attenuation-associated mutations to the actual mechanism of attenuation, nor the potential for reverse mutations to revert any of the vaccine candidates to the virulent biological phenotype of the wild-type dengue virus are known for any of these four vaccine candidates. An understanding of the attenuation markers
5 of a vaccine candidate is critical for the prediction of its stability and safety.

Accordingly, there is a need for avirulent, yet immunogenic, dengue viruses to be used in the development of dengue virus vaccines to confer protection against one or more dengue virus serotypes. What would be ideal is a vaccine that would
10 simultaneously protect an individual against several virulent strains of this potentially dangerous family (Flaviviridae) of viruses. Therefore, a tetravalent vaccine that can be used to immunize an individual against all four dengue serotypes is particularly needed.

SUMMARY OF THE INVENTION

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Immunogenic flavivirus chimeras, a dengue-2 virus backbone for preparing the flavivirus chimeras and methods for producing the flavivirus chimeras are described. The immunogenic flavivirus chimeras are provided, alone or in combination, in a pharmaceutically acceptable carrier as immunogenic compositions to minimize, inhibit,
20 or immunize individuals against infection by one or more flaviviruses or flaviviral strains, particularly strains of the dengue virus serotypes DEN-1, DEN-2, DEN-3 and DEN-4. When combined, the immunogenic flavivirus chimeras may be used as multivalent vaccines to confer simultaneous protection against infection by more than one species or strain of flavivirus. Preferably, the flavivirus chimeras are combined in
25 an immunogenic composition useful as a tetravalent vaccine against the four known dengue virus serotypes. The nucleic acid sequence for each of the DEN-1, DEN-3 and DEN-4 viruses is also provided, for use as probes to detect dengue virus in a biological sample.

The avirulent, immunogenic flavivirus chimeras provided herein contain the nonstructural protein genes of the attenuated dengue-2 virus, or the equivalent thereof, and one or more of the structural protein genes or immunogenic portions thereof of the flavivirus against which immunogenicity is to be conferred. For example, the preferred chimera contains the attenuated dengue-2 virus PDK-53 genome as the viral backbone, and the structural protein genes encoding capsid, premembrane/membrane, or envelope of the PDK-53 genome, or combinations thereof, are replaced with the corresponding structural protein genes from a flavivirus to be protected against, such as a different flavivirus or a different dengue virus serotype. The resulting viral chimera has the functional properties of the attenuated dengue-2 virus and is therefore avirulent, but expresses antigenic epitopes of the structural gene products and is therefore immunogenic.

In another embodiment, the preferred chimera is a nucleic acid chimera comprising a first nucleotide sequence encoding nonstructural proteins from an attenuated dengue-2 virus, and a second nucleotide sequence encoding a structural protein from a second flavivirus. In a further preferred embodiment, the attenuated dengue-2 virus is vaccine strain PDK-53. In a further preferred embodiment, the structural protein can be the C, prM or E protein of a flavivirus. Examples of flaviviruses from which the structural protein may be selected include, but are not limited to, dengue-1 virus, dengue-2 virus, dengue-3 virus, dengue-4 virus, West Nile virus, Japanese encephalitis virus, St. Louis encephalitis virus, yellow fever virus and tick-borne encephalitis virus. In a further embodiment, the structural protein may be selected from non-flavivirus species that are closely related to the flaviviruses, such as hepatitis C virus.

In evaluating the chimeric virus of the invention, it was unexpectedly discovered that the avirulence of the attenuated PDK-53 virus strain is attributable to the presence of specific amino acid substitution mutations in the nonstructural proteins and a nucleotide substitution mutation in the 5' noncoding region. This nucleotide

substitution mutation occurs in the stem of a stem-loop structure that is conserved in all four dengue serotypes. In particular, a single mutation at NS1-53, a double mutation at NS1-53 and at 5'NC-57, a double mutation at NS1-53 and at NS3-250, and a triple mutation at NS1-53, at 5'NC-57 and at NS3-250, can provide the attenuated DEN-2 virus of the present invention.

Furthermore, the genome of any dengue-2 virus containing non-conservative amino acid substitutions at these loci can be used as the backbone in the avirulent chimeras described herein. Furthermore, other flavivirus genomes containing analogous mutations at the same loci, after amino acid sequence or nucleotide sequence alignment and stem structure analysis can also be used as the backbone structure and are defined herein as being equivalent to attenuating mutations of the dengue-2 PDK-53 genome.

The backbone, that region of the chimera that comprises the 5' and 3' noncoding regions and the region encoding the nonstructural proteins, can also contain further mutations to maintain stability of the avirulent phenotype and to reduce the possibility that the avirulent virus or chimera might revert back to the virulent wild-type virus. For example, a second mutation in the stem of the stem/loop structure in the 5' noncoding region will provide additional stability, if desired.

These chimeric viruses can comprise nucleotide and amino acid substitutions, deletions or insertions in their structural and nonstructural proteins in addition to those specifically described herein.

The structural and nonstructural proteins of the invention are to be understood to include any protein comprising or any gene encoding the sequence of the complete protein, an epitope of the protein, or any fragment comprising, for example, two or more amino acid residues thereof.

The present invention also provides a method for making the chimeric viruses of this invention using recombinant techniques, by inserting the required substitutions into the appropriate backbone genome.

5 The present invention also provides compositions comprising a pharmaceutically acceptable carrier and attenuated chimeric viruses of this invention which contain amino acid sequences derived from other dengue virus serotypes, other flavivirus species or other closely related species, such as hepatitis C virus. As an object of the invention, the amino acid sequences derived from other dengue virus
10 serotypes, other flavivirus species or other closely related species, such as hepatitis C virus, are expressed in a host, host cell or cell culture. As a further object of the invention, proteins or polypeptides comprising the amino acid sequences derived from other dengue virus serotypes, other flavivirus species or other closely-related species, can act as immunogens and, thus, be used to induce an immunogenic response against
15 other dengue virus serotypes, other flavivirus species or other closely related species.

 The present invention also provides compositions comprising a pharmaceutically acceptable carrier, one or more attenuated chimeric viruses of this invention and further immunizing compositions. Examples of such further immunizing
20 compositions include, but are not be limited to, dengue virus vaccines, yellow fever virus vaccines, tick-borne encephalitis virus vaccines, Japanese encephalitis virus vaccines, West Nile virus vaccines, hepatitis C virus vaccines or other virus vaccines. Such vaccines may be live attenuated virus vaccines, killed virus vaccines, subunit vaccines, recombinant DNA vector vaccines or any combination thereof.

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A distinct advantage of the current invention is that it provides for mixtures of attenuated flavivirus chimeras to be used as vaccines in order to impart immunity against several flavivirus species simultaneously.

Thus, an object of the current invention is to provide a virus chimera containing amino acid or nucleotide substitutions which retain immunogenicity of the virus while preventing any pathogenic effects of the virus.

5 Another object of the present invention is to provide nucleic acid chimeras comprising nucleotide sequence from an attenuated dengue-2 virus and nucleotide sequence from a second flavivirus, wherein the nucleotide sequence from the second flavivirus directs the synthesis of flavivirus antigens.

10 Another object of the present invention is to provide compositions for vaccines comprising more than one flavivirus species.

Another object of the present invention is to provide a method for making immunogenic or vaccine compositions using recombinant techniques by inserting the
15 required substitutions into an appropriate flavivirus genome.

Another object of the invention is to provide compositions and methods for imparting immunity against more than one flavivirus simultaneously.

20 Another object of the invention is to provide nucleic acid probes and primers for use in any of a number of rapid genetic tests that are diagnostic for each of the vaccine viruses of the current invention. This object of the invention may be embodied in polymerase chain reaction assays, hybridization assays or other nucleic acid sequence detection techniques known to the art. A particular embodiment of this object is an
25 automated PCR-based nucleic acid detection system.

These and other objects, features and advantages of the present invention will become apparent after review of the following detailed description of the disclosed embodiments and the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 schematically shows the genomic organization of the chimeric DEN-2/DEN-1 viruses. Designations of the chimeras are based on the DEN-2 virus-specific infectious clone backbones and the structural genes (C-prM-E) insert of DEN-1 viruses. Underlined letters of the backbone and insert viruses are used in the designations. D2/1 indicates DEN-2/DEN-1 chimera; the first letter following the hyphen is the DEN-2 viral backbone, parent 16681 (P), PDK53-E (E), or PDK53-V (V); the last letter indicates the structural genes from the parental DEN-1 16007 (P) strain or its vaccine derivative, strain PDK-13 (V). The PDK53-E backbone contains three DEN-2 PDK-53 virus-specific amino acid mutations (NS1-53-Asp, NS2A-181-Phe, and NS4A-75-Ala) as well as the 5'NC-57 mutation of PDK-53 virus. The PDK53-V backbone contains these same PDK-53 virus-specific loci plus the additional PDK-53 virus-specific NS3-250-Val locus.

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FIGURES 2A and 2B show the growth characteristics of the chimeric DEN-2/DEN-1 viruses in LLC-MK₂ cells. Stippled bars indicate DEN-1 16007 virus and the chimeric viruses expressing the structural proteins of DEN-1 16007 virus. Bars with stripes indicate DEN-1 PDK-13 virus and the chimeric viruses expressing structural proteins of PDK-13 virus. Blank bars indicate the three DEN-2 backbone viruses derived from infectious clones of DEN-2 16681 virus (P48) and the two variants (PDK53-E and PDK53-V; E48 and V48, respectively). Figure 2A: Mean (\pm SD) plaque diameters. Values were calculated from ten individual plaques of each virus on day 10 after infection. pp: pinpoint-size plaques less than 1 mm. Figure 2B: Temperature sensitivity (*ts*) and peak titers of chimeric viruses on day 8 or 10 after infection. The *ts* scores were based on the reduction of the virus titers at 38.7°C versus those at 37°C (-, +, 2+ and 3+ indicate titer reduction of less than or equal to 60%, 61-90%, 91-99%, >99%, respectively, calculated from at least three experiments). The graph bar heights represent the log₁₀ titers of the viruses at 37°C. The multiplicity of infection (m.o.i.) was approximately 0.001 PFU/cell.

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FIGURE 3 shows the growth curves of DEN-1 16007, DEN-1 PDK-13, DEN-2 16681-P48, DEN-2 PDK53-E48, DEN-2 PDK53-V48 and chimeric DEN-2/DEN-1 viruses in C6/36 cells. Cells were infected at an approximate m.o.i. of 0.001 PFU/ml.

- 5 FIGURES 4A-C. Figure 4A: Mean plaque diameters \pm SD in millimeters (n=12) of DEN-2 16681, PDK-53 and recombinant 16681/PDK-53 viruses at nine days after infection in LLC-MK₂ cells. Figure 4B: Peak replication titers at 6-8 days after infection of LLC-MK₂ cells at a m.o.i. of approximately 0.001 PFU/cell in a single experiment. Temperature sensitivity (*ts*) scores for viruses grown at 37 °C or 38.7 °C
- 10 in LLC-MK₂ cells are shown above the graph bars for peak replication titers. Scores of (-), (+/-) and (+) indicate less than 81%, 81-89% and 90-97% reduction in viral titer, respectively, at 38.7 °C. Scores were determined at eight days after infection. Figure 4C: Average peak replication titers at 12 days after infection of C6/36 cells at a multiplicity of approximately 0.001 PFU/cell in two independent experiments.
- 15 Individual peak titers from the two experiments are indicated by vertical lines in each graph bar. The numerical designations for recombinant Px and Vx viruses (where x = 5'NC, NS1, and/or NS3 loci) indicate parental (P in virus designation) 16681 virus-specific loci engineered into the PDK-53 virus-specific infectious cDNA clone or reciprocal candidate PDK-53 vaccine (V in virus designation) virus-specific loci
- 20 engineered into the 16681 clone, respectively. Cognate viruses are indicated in all three graphs by graph bars of identical solid or cross-hatching pattern. The cognate for P5 virus is V13 virus, assuming that the viral phenotype is determined predominantly by the 5'NC-57, NS1-53 and NS3-250 loci. Both P5 and V13 viruses contain the 5'NC-57-C (16681), NS1-53-Asp (PDK-53) and NS3-250-Val (PDK-53) loci within the genetic
- 25 backgrounds of PDK-53 and 16681 viruses, respectively.

DETAILED DESCRIPTION OF THE INVENTION

The following description includes the best presently contemplated mode of carrying out the invention. This description is made for the purpose of illustrating the general principles of the inventions and should not be taken in a limiting sense.

Immunogenic flavivirus chimeras, a dengue-2 virus or dengue-2 virus equivalent backbone for preparing the flavivirus chimeras of this invention and methods for preparing the flavivirus chimeras are provided herein. The immunogenic flavivirus chimeras are useful, alone or in combination, in a pharmaceutically acceptable carrier as immunogenic compositions to minimize, inhibit, or immunize individuals against infection by one or more flaviviruses or flaviviral strains, particularly strains of the dengue virus serotypes DEN-1, DEN-2, DEN-3 and DEN-4. When combined, the immunogenic flavivirus chimeras may be used as a multivalent vaccine to confer simultaneous protection against infection. Preferably, the dengue virus chimeras are combined in an immunogenic composition useful as a tetravalent vaccine against the four known dengue virus serotypes.

Immunogenic flavivirus chimeras of the current invention are also useful, in combination with avirulent virus strains, in a pharmaceutically acceptable carrier, as immunogenic compositions to minimize, inhibit or immunize individuals against infection by multiple pathogenic species. For example, one or more of the immunogenic flavivirus chimeras of the current invention can be combined with avirulent virus serotypes of selected flaviviruses to provide a safe and effective tetravalent vaccine against the four known dengue virus serotypes. In a further embodiment, the flavivirus chimeras of the current invention may be combined with avirulent virus vaccines to provide a safe and effective vaccine against infection by multiple pathogenic species.

The present invention also provides compositions comprising a pharmaceutically acceptable carrier, one or more attenuated chimeric viruses of this invention and further immunizing compositions. Examples of such further immunizing compositions include, but are not limited to, dengue virus vaccines, yellow fever vaccines, tick-borne encephalitis vaccines, Japanese encephalitis vaccines, West Nile virus vaccines, hepatitis C virus vaccines or other virus vaccines. Such vaccines may be live attenuated virus vaccines, killed virus vaccines, subunit vaccines, recombinant DNA vector vaccines or any combination thereof.

10 The nucleic acid sequence for each of the DEN-1, DEN-3 and DEN-4 viruses is also provided for use as probes to detect dengue virus in a biological sample.

Chimeras of the present invention can comprise the backbone of the dengue-2 virus of an attenuated dengue-2 virus and further nucleotide sequences selected from more than one dengue virus serotype, other flavivirus species, other closely related species, such as hepatitis C virus, or any combination thereof. These chimeras can be used to induce an immunogenic response against more than one species selected from the dengue virus serotypes, flavivirus species, other closely related species or any combination thereof.

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In another embodiment, the preferred chimera is a nucleic acid chimera comprising a first nucleotide sequence encoding nonstructural proteins from an attenuated dengue-2 virus, and a second nucleotide sequence encoding a structural protein from a second flavivirus. In a further preferred embodiment, the attenuated dengue-2 virus is vaccine strain PDK-53. In a further preferred embodiment, the structural protein can be the C protein of a flavivirus, the prM protein of a flavivirus, the E protein of a flavivirus, or any combination thereof. Examples of flaviviruses from which the structural protein may be selected include, but are not limited to, dengue-1 virus, dengue-2 virus, dengue-3 virus, dengue-4 virus, West Nile virus, Japanese encephalitis virus, St. Louis encephalitis virus, yellow fever virus and tick-

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borne encephalitis virus. In a further embodiment, the structural protein may be selected from non-flavivirus species that are closely related to the flaviviruses, such as hepatitis C virus.

- 5 The terms "a," "an" and "the" as used herein are defined to mean one or more and include the plural unless the context is inappropriate.

 The term "residue" is used herein to refer to an amino acid (D or L) or an amino acid mimetic that is incorporated into a peptide by an amide bond. As such, the amino
10 acid may be a naturally occurring amino acid or, unless otherwise limited, may encompass known analogs of natural amino acids that function in a manner similar to the naturally occurring amino acids (*i.e.*, amino acid mimetics). Moreover, an amide bond mimetic includes peptide backbone modifications well known to those skilled in the art.

15 Furthermore, one of skill in the art will recognize that individual substitutions, deletions or additions in the amino acid sequence, or in the nucleotide sequence encoding for the amino acids, which alter, add or delete a single amino acid or a small percentage of amino acids (typically less than 5%, more typically less than 1%) in an
20 encoded sequence are conservatively modified variations, wherein the alterations result in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. The following six groups each contain amino acids that are conservative substitutions for one another:

- 25 1) Alanine (A), Serine (S), Threonine (T);
 2) Aspartic acid (D), Glutamic acid (E);
 3) Asparagine (N), Glutamine (Q);
 4) Arginine (R), Lysine (K);
 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and
30 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

As used herein, the terms “virus chimera,” “chimeric virus,” “flavivirus chimera” and “chimeric flavivirus” means an infectious construct of the invention comprising a portion of the nucleotide sequence of a dengue-2 virus and further nucleotide sequence that is not from the same dengue-2 virus. Thus, examples of further nucleotide sequence include, but are not limited to, sequences from dengue-1 virus, dengue-2 virus, dengue-3 virus, dengue-4 virus, West Nile virus, Japanese encephalitis virus, St. Louis encephalitis virus, tick-borne encephalitis virus, yellow fever virus and any combination thereof.

As used herein, “infectious construct” indicates a virus, a viral construct, a viral chimera, a nucleic acid derived from a virus or any portion thereof, which may be used to infect a cell.

As used herein, “nucleic acid chimera” means a construct of the invention comprising nucleic acid comprising a portion of the nucleotide sequence of a dengue-2 virus and further nucleotide sequence that is not of the same origin as the nucleotide sequence of the dengue-2 virus. Correspondingly, any chimeric flavivirus or flavivirus chimera of the invention is to be recognized as an example of a nucleic acid chimera.

The structural and nonstructural proteins of the invention are to be understood to include any protein comprising or any gene encoding the sequence of the complete protein, an epitope of the protein, or any fragment comprising, for example, two or more amino acid residues thereof.

Nucleotide sequences of the RNA genome of the viruses and chimeras of the current invention are recited in the sequence listings in terms of DNA.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one having ordinary skill in the art to which this invention pertains. Although other materials and methods similar or equivalent to

those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

Flavivirus Chimeras

5 Dengue virus types 1-4 (DEN-1 to DEN-4) are mosquito-borne flavivirus pathogens. The flavivirus genome contains a 5'-noncoding region (5'-NC), followed by a capsid protein (C) encoding region, followed by a premembrane/membrane protein (prM) encoding region, followed by an envelope protein (E) encoding region, followed by the region encoding the nonstructural proteins (NS1-NS2A-NS2B-NS3-NS4A-
10 NS4B-NS5) and finally a 3' noncoding region (3'NC). The viral structural proteins are C, prM and E, and the nonstructural proteins are NS1-NS5. The structural and nonstructural proteins are translated as a single polypeptide and processed by cellular and viral proteases.

15 The flavivirus chimeras of the invention are constructs formed by fusing non-structural protein genes from one type, or serotype, of dengue virus or virus species of the flaviviridae, with protein genes, for example, structural protein genes, from a different type, or serotype, of dengue virus or virus species of the flaviviridae. Alternatively, a flavivirus chimera of the invention is a construct formed by fusing non-
20 structural protein genes from one type, or serotype, of dengue virus or virus species of the flaviviridae, with further nucleotide sequences that direct the synthesis of polypeptides or proteins selected from other dengue virus serotypes or other viruses of the flaviviridae.

25 The avirulent, immunogenic flavivirus chimeras provided herein contain the nonstructural protein genes of the attenuated dengue-2 virus, or the equivalent thereof, and one or more of the structural protein genes, or antigenic portions thereof, of the flavivirus against which immunogenicity is to be conferred. Suitable flaviviruses include, but are not limited to those listed in Table 1.

Other suitable flaviviruses for use in constructing the flavivirus chimeras of the invention are wild-type, virulent DEN-1 16007 (SEQ ID NO:1; SEQ ID NO:2), DEN-2 16681 (SEQ ID NO:13; SEQ ID NO:14), DEN-3 16562 (SEQ ID NO:19; SEQ ID NO:20) and DEN-4 1036 (SEQ ID NO:23; SEQ ID NO:24) and attenuated, vaccine-strain DEN-1 PDK-13 (SEQ ID NO:3; SEQ ID NO:4), DEN-2 PDK-53 (SEQ ID NO:15; SEQ ID NO:16), DEN-3 PMK-30/FRhL-3 (SEQ ID NO:21; SEQ ID NO:22) and DEN-4 PDK-48 (SEQ ID NO:25; SEQ ID NO:26). Further suitable flaviviruses, or variants of the above listed flaviviruses, are described herein. Genetic differences between the DEN-1, DEN-2, DEN-3 and DEN-4 wild type/attenuated virus pairs are shown in Tables 2-5 along with changes in the amino acid sequences encoded by the viral genomes.

The sequence listings for DEN-2 PDK-53 provided herein (SEQ ID NO:15; SEQ ID NO:16) correspond to the DEN-2 PDK-53-V variant, wherein genome nucleotide position 5270 is mutated from an A to a T and amino acid position 1725 of the polyprotein or amino acid position 250 of the NS3 protein contains a valine residue. The DEN-2 PDK-53 variant without this nucleotide mutation, DEN-2 PDK-53-E, differs from PDK-53-V only in this one position. DEN-2 PDK-53-E has an A at nucleotide position 5270 and a glutamate at polyprotein amino acid position 1725, NS3 protein amino acid position 250 (Table 3).

The sequence listings for DEN-3 16562 provided herein (SEQ ID NO:21; SEQ ID NO:22) correspond to the variant wherein genome nucleotide position 1521 is a T and amino acid position 476 of the polyprotein or amino acid position 196 of the E protein contain a leucine. A second variant, present in DEN-3 16562 cultures has a T at nucleotide position 1521 and amino acid position 476 of the polyprotein or amino acid position 196 of the E protein contain a serine (Table 4).

The sequence listings for DEN-4 PDK-48 (SEQ ID NO:25; SEQ ID NO:26) correspond to the variant wherein genome nucleotide positions: 6957 is a T and amino

acid position 2286 of the polyprotein and amino acid position 44 of NS4B protein is a phenylalanine, 7546 is a T and amino acid position 2366 of the polyprotein and amino acid position 240 of NS4B protein is a valine, and 7623 is a T and amino acid position 2508 of the polyprotein and amino acid position 21 of NS5 protein is a tyrosine (Table 5).

Throughout the text, designations of the chimeras are based on the DEN-2 virus-specific infectious clone backbones and the structural genes (prM-E or C-prM-E) insert of other flaviviruses. Each designation begins with DEN-2 for the dengue-2 backbone, followed by the strain from which the structural genes are inserted. The particular backbone variant is reflected in the next letter. The particular DEN-2 backbone variant from which the chimera was constructed is indicated by the following letter placed after a hyphen, parent 16681 (P), PDK53-E (E), or PDK53-V (V); the last letter indicates the C-prM-E structural genes from the parental (P) strain or its vaccine derivative (V) or the prM-E structural genes from the parental (P1) or its vaccine derivative (V1). For example; DEN-2/1-VP (SEQ ID NO:5; SEQ ID NO:6) denotes the chimera comprising the attenuated DEN-2 PDK-53V backbone comprising a valine at NS3-250 and the C-prM-E genes from wild-type DEN-1 16007; DEN-2/1-VV (SEQ ID NO:7; SEQ ID NO:8) denotes the DEN-2 PDK-53V backbone with the vaccine strain of dengue-1, DEN-1 PDK-13; DEN-2/1-VP1 (SEQ ID NO:27; SEQ ID NO:28) denotes the DEN-2 PDK-53V backbone and the prM-E genes from wild-type DEN-1 16007; DEN-2/3-VP1 (SEQ ID NO:9; SEQ ID NO:10) denotes the DEN-2 PDK-53V backbone and the prM-E genes from wild-type DEN-3 16562; DEN-2/4-VP1 (SEQ ID NO:11; SEQ ID NO:12) denotes the DEN-2 PDK-53V backbone and the prM-E genes from wild-type DEN-4 1036; and DEN-2/WN-PP1 (SEQ ID NO:17; SEQ ID NO:18) denotes the DEN-2 16681 backbone and the prM-E genes from West Nile NY99. Other chimeras of the present invention, denoted in the same manner, are clearly defined herein by the disclosed sequences. For instance, DEN-2/1-PV is defined herein as consisting of the wild-type dengue-2 backbone, DEN-2 16681, and the C-prM-E genes of the vaccine strain of dengue-1, DEN-1 PDK-13.

The preferred chimera of the invention, for example, contains the attenuated dengue-2 virus PDK-53 genome as the viral backbone, in which the structural protein genes encoding C, prM and E proteins of the PDK-53 genome, or combinations thereof, are replaced with the corresponding structural protein genes from a flavivirus to be protected against, such as a different flavivirus or a different dengue virus strain. Newly discovered flaviviruses or flavivirus pathogens can also be incorporated into the DEN-2 backbone. Genetic recombinations with related viruses such as hepatitis C virus (HCV) could also be used to produce the chimeras of this invention. The resulting viral chimera has the functional properties of the attenuated dengue-2 virus and is therefore avirulent, but expresses antigenic epitopes of the structural gene products and is therefore immunogenic.

Nine nucleotide mutations between the genomes of the wild type DEN-2 16681 virus and two attenuated PDK-53 virus strains are identified herein (Table 3). Three of these mutations are silent mutations in that they do not result in the production of an amino acid that differs from the amino acid in the same position in the wild type virus. The first mutation is a C-to-T (wild type-to-PDK-53) nucleotide mutation at genome nucleotide position 57 (nt 57) in the 5' noncoding region. The second mutation is a A-to-T mutation at genome nucleotide position 524, encoding the amino acid substitution Asp-to-Val in the structural protein premembrane region, prM-29.

In the nonstructural protein regions, a Gly-to-Asp (wild type-to-PDK-53) mutation was discovered at nonstructural protein NS1-53 (genome nucleotide position 2579); a Leu-to-Phe (wild type-to-PDK-53) mutation was discovered at nonstructural protein NS2A-181 (genome nucleotide position 4018); a Glu-to-Val (wild type-to-PDK-53) mutation was discovered at nonstructural protein NS3-250 (genome nucleotide position 5270); and a Gly-to-Ala mutation (wild type-to-PDK-53) was discovered at nonstructural protein NS4A-75 (genome nucleotide position 6599).

The attenuated PDK-53 virus strain has a mixed genotype at genome nt 5270. A significant portion (approximately 29%) of the virus population encodes the non-mutated NS3-250-Glu that is present in the wild type DEN-2 16681 virus rather than the NS3-250-Val mutation. As both genetic variants are avirulent, this mutation may not be necessary in an avirulent chimera.

It was unexpectedly discovered that the avirulence of the attenuated PDK-53 virus strain can be attributed to the presence of specific mutations in the nucleotide sequence encoding nonstructural proteins and in the 5' noncoding region (Example 5). In particular, a single mutation at NS1-53, a double mutation at NS1-53 and at 5'NC-57, a double mutation at NS1-53 and at NS3-250 and a triple mutation at NS1-53, at 5'NC-57 and at NS3-250, result in attenuation of the DEN-2 virus. Therefore, the genome of any dengue-2 virus containing such non-conservative amino acid substitutions or nucleotide substitutions at these loci can be used as the backbone in the avirulent chimeras described herein. The backbone can also contain further mutations to maintain stability of the avirulent phenotype and to reduce the possibility that the avirulent virus or chimera might revert back to the virulent wild-type virus. For example, a second mutation in the stem of the stem/loop structure in the 5' noncoding region will provide additional avirulent phenotype stability, if desired. The stem of the stem-loop structure is composed of nucleotide residues 11-16 (CUACGU) (SEQ ID NO:29) and nucleotide residues 56-61 (ACGUAG) (SEQ ID NO:30) of the dengue-2 virus RNA sense sequence, wherein the underlined nucleotide is C in wild-type DEN-2 16681 virus and U in PDK-53 virus. Mutations to this region disrupt potential secondary structures important for viral replication. In particular, mutations in the 5' noncoding region have the ability to disrupt the function of the positive-sense RNA strand and the function of the negative-sense strand during replication. A single mutation in this short (only 6 nucleotide residues in length) stem structure in both DEN and Venezuelan equine encephalitis viruses disrupts the formation of the hairpin structure (Kinney et al., *Virology* 67, 1269-1277, (1993)). Further mutations in this stem structure decrease the possibility of reversion at this locus, while maintaining

virus viability. Furthermore, flavivirus genomes containing an analogous stem structure that consists of short nucleotide sequences (stems consisting of 6 or more base pairs in the stem-loop structure) located in the 5' noncoding region and having one or more mutations in the stem structure may also be useful as the backbone structure of this invention.

Such mutations may be achieved by site-directed mutagenesis using techniques known to those skilled in the art. Furthermore, other flavivirus genomes containing analogous mutations at the same loci after amino acid sequence alignment, can be used as the backbone structure of the chimera of this invention and are defined herein as being equivalent to the dengue-2 PDK-53 genome. It will be understood by those skilled in the art that the virulence screening assays, as described herein and as are well known in the art, can be used to distinguish between virulent and avirulent backbone structures.

Construction of Flavivirus Chimeras

The flavivirus chimeras described herein can be produced by splicing one or more of the structural protein genes of the flavivirus against which immunity is desired into a PDK-53 dengue virus genome backbone, or the equivalent thereof as described above, using recombinant engineering techniques well known to those skilled in the art to remove the corresponding PDK-53 gene and replace it with the desired gene. Alternatively, using the sequences provided in the sequence listing, the nucleic acid molecules encoding the flavivirus proteins may be synthesized using known nucleic acid synthesis techniques and inserted into an appropriate vector. An avirulent, immunogenic virus is therefore produced using recombinant engineering techniques known to those skilled in the art.

As mentioned above, the gene to be inserted into the backbone encodes a flavivirus structural protein. Preferably the flavivirus gene to be inserted is a gene encoding a C protein, a PrM protein and/or an E protein. The sequence inserted into

the dengue-2 backbone can encode both the PrM and E structural proteins. The sequence inserted into the dengue-2 backbone can encode the C, prM and E structural proteins. The dengue virus backbone is the PDK-53 dengue-2 virus genome and includes either the spliced genes that encode the C, PrM and/or E structural proteins of dengue-1 (DEN-2/1), the spliced genes that encode the PrM and/or E structural proteins of dengue-3 (DEN-2/3), or the spliced genes encode the PrM and/or E structural proteins of dengue-4 (DEN-2/4). In a particular embodiment of this invention, the spliced gene that encodes the structural protein of dengue-3 virus directs the synthesis of an E protein that contains a leucine at amino acid position 345.

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In a particular embodiment, the chimera of this invention encodes the C structural protein of dengue-2 virus and directs the synthesis of a C protein that contains a serine at amino acid position 100 and comprises a spliced gene encoding the structural proteins of dengue-4 which directs the synthesis of an E protein that contains a leucine at amino acid position 447.

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In a further embodiment, the chimera of this invention encodes the C structural protein of dengue-2 virus and directs the synthesis of a C protein that contains a serine at amino acid position 100 and comprises a spliced gene encoding the structural proteins of dengue-4 which directs the synthesis of an E protein that contains a leucine at amino acid position 447 and a valine at amino acid position 364. The structural proteins described herein can be present as the only flavivirus structural protein or in any combination of flavivirus structural proteins in a viral chimera of this invention.

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The chimeras of this invention are engineered by recombination of full genome-length cDNA clones derived from both DEN-2 16681 wild type virus and either of the PDK-53 dengue-2 virus variants (-E or -V(SEQ ID NO:15)). The uncloned PDK-53 vaccine contains a mixture of two genotypic variants, designated herein as PDK53-E and PDK53-V. The PDK53-V variant contains all nine PDK-53 vaccine-specific nucleotide mutations, including the Glu-to-Val mutation at amino acid position NS3-

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250. The PDK53-E variant contains eight of the nine mutations of the PDK-53 vaccine and the NS3-250-Glu of the parental 16681 virus. Infectious cDNA clones are constructed for both variants, and viruses derived from both clones are attenuated in mice. The phenotypic markers of attenuation of DEN-2 PDK-53 virus include small
5 plaque size, temperature sensitivity (particularly in LLC-MK₂ cells), limited replication (particularly in C6/36 cells), attenuation for newborn mice (specifically loss of neurovirulence for suckling mice) and decreased incidence of viremia in monkeys. The chimeras that are useful as vaccine candidates are constructed in the genetic backgrounds of the two DEN-2 PDK-53 variants which all contain mutations in
10 nonstructural regions of the genome, including 5'NC-57 C-to-T (16681-to-PDK-53) in the 5' noncoding region, as well as mutations in the amino acid sequence of the nonstructural proteins, such as, for example, NS1-53 Gly-to-Asp and NS3-250 Glu-to-Val.

15 Suitable chimeric viruses or nucleic acid chimeras containing nucleotide sequences encoding structural proteins of other flaviviruses or dengue virus serotypes can be evaluated for usefulness as vaccines by screening them for the foregoing phenotypic markers of attenuation that indicate avirulence and by screening them for immunogenicity. Antigenicity and immunogenicity can be evaluated using *in vitro* or
20 *in vivo* reactivity with flavivirus antibodies or immunoreactive serum using routine screening procedures known to those skilled in the art.

Flavivirus Vaccines

25 The preferred chimeric viruses and nucleic acid chimeras provide live, attenuated viruses useful as immunogens or vaccines. In a preferred embodiment, the chimeras exhibit high immunogenicity while at the same time producing no dangerous pathogenic or lethal effects.

30 Until now, an effective vaccine against all strains of dengue virus has been unavailable. Individual live attenuated vaccine candidates for all four serotypes have

been developed by serial passage of wild-type viruses in primary dog kidney (PDK) cells or other cell types. As described above, the PDK-53 virus is a useful dengue vaccine candidate. However, a vaccine derived from PDK-53 would only provide immunity against the DEN-2 serotype.

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To prevent the possible occurrence of DHF/DSS in patients vaccinated against only one serotype of dengue virus, a tetravalent vaccine is needed to provide simultaneous immunity for all four serotypes of the virus. A tetravalent vaccine is produced by combining dengue-2 PDK-53 with the dengue-2/1, dengue-2/3, and
10 dengue-2/4 chimeras described above in a suitable pharmaceutical carrier for administration as a multivalent vaccine.

The chimeric viruses or nucleic acid chimeras of this invention can comprise the structural genes of either wild-type or attenuated virus in a virulent or an attenuated
15 DEN-2 virus backbone. For example, the chimera may express the structural protein genes of wild-type DEN-1 16007 virus or its candidate PDK-13 vaccine derivative in either of the DEN-2 PDK-53 backgrounds.

As described in Example 1, all of the chimeric DEN-2/1 viruses containing the
20 C, prM and E proteins of either DEN-1 16007 virus (DEN-2/1-EP and -VP chimeras) or PDK-13 virus (DEN-2/1-EV and -VV (SEQ ID NO:7) chimeras) in the backbones of DEN-2 PDK-53 retain all of the phenotypic attenuation markers of the DEN-2 PDK-53 virus. The chimeric DEN-2/1-EP and -VP (SEQ ID NO:5) viruses, which contain the C, prM and E proteins of DEN-1 16007 virus are more genetically stable after passing in
25 cell culture than the DEN-2/1-EV and -VV viruses. The immunogenicity of the chimeric viruses expressing the structural proteins of DEN-1 16007 virus was higher as compared with the neutralizing antibody titers elicited by the PDK-13 vaccine virus and the chimeras expressing the structural proteins of the PDK-13 virus. Thus, the chimeric DEN-2/1-EP and -VP viruses, which express the structural genes of wild-type DEN-1
30 16007 virus within the genetic background of the two DEN-2 PDK-53 variants, are

potential DEN-1 vaccine candidates that are superior to the candidate PDK-13 vaccine. These two chimeras replicate well in LLC-MK₂ cells and retain the attenuation markers associated with DEN-2 PDK-53 virus, including small plaque size, temperature sensitivity, restricted replication in mosquito cells and attenuation for mice. They are at least as immunogenic as wild-type DEN-1 16007 virus in mice.

Other examples, such as DEN-2/3 and DEN-2/4 chimeras, in Examples 2-4, also showed that chimeric viruses containing structural protein genes from wild-type DEN-3 or DEN-4 virus within the DEN-2 PDK-53 backbones, are suitable vaccine candidates which retain all of the attenuated phenotypic markers of the DEN-2 PDK-53 viruses (Table 14), while providing immunogenicity against DEN-3 or DEN-4 virus. The strategy described herein of using a genetic background that contains the determinants of attenuation in nonstructural regions of the genome to express the structural protein genes of heterologous viruses has lead to development of live, attenuated flavivirus vaccine candidates that express wild-type structural protein genes of optimal immunogenicity. Thus, vaccine candidates for immunogenic variants of multiple flaviviral pathogens can be designed.

Viruses used in the chimeras described herein are typically grown using techniques known in the art. Virus plaque titrations are then performed and plaques counted in order to assess the viability and phenotypic characteristics of the growing cultures. Wild type viruses are passaged through cultured cell lines to derive attenuated candidate starting materials.

Chimeric infectious clones are constructed from the various dengue serotype clones available. The cloning of virus-specific cDNA fragments can also be accomplished, if desired. The cDNA fragments containing the structural protein or nonstructural protein genes are amplified by reverse transcriptase-polymerase chain reaction (RT-PCR) from dengue virus RNA with various primers. Amplified fragments are cloned into the cleavage sites of other intermediate clones. Intermediate, chimeric

dengue virus clones are then sequenced to verify the accuracy of the inserted dengue virus-specific cDNA.

Full genome-length chimeric plasmids constructed by inserting the structural protein or nonstructural protein gene region of dengue serotype viruses into vectors are obtainable using recombinant techniques well known to those skilled in the art.

Nucleotide and Amino Acid Analysis

The nucleotide sequence for DEN-2 16681 and corresponding PDK-53-V are provided in SEQ ID NO:13 and SEQ ID NO:15, respectively. Amino acid sequences for DEN-2 16681 and corresponding PDK-53-V are provided in SEQ ID NO:14 and SEQ ID NO:16. The -E variant of PDK-53, which varies from PDK-53-V at nucleotide position 5270 and amino acid position 1725 of the polypeptide is further described in Table 3. A comparison of the critical nucleotide and amino acid substitutions that have been discovered between the parent strain and the attenuated virus is shown in Table 3. The sequence of the DEN-2 cDNA amplicons was amplified from DEN-2 viral genomic RNA by reverse transcriptase-polymerase chain reaction (RT-PCR).

Unlike PDK-53, which contains no amino acid mutations in the E protein relative to wild type dengue-2 virus, the Mahidol DEN-1, DEN-3 and DEN-4 attenuated viruses all have amino acid mutations in the E protein (Tables 2,4 & 5). The wild-type DEN-3 16562 listed in the sequence listing (nucleotide sequence, SEQ ID NO:19; amino acid sequence, SEQ ID NO:20) was shown to comprise traces of a variant comprising a T at nucleotide position 1521 which directs incorporation of a leucine at polypeptide position 476, amino acid residue position 476 of the E protein.

Each of the latter three viruses possess a Glu-to-Lys (parent-to-vaccine) mutation in the E protein, although the mutation is located at a different amino acid residue in the E protein. This substitution causes a shift from a negatively charged

amino acid to a positively charged one. The Glu-to-Lys substitution in the E protein of DEN-4 vaccine virus was the only mutation present in the E protein, while the E proteins of DEN-1 and DEN-3 vaccine viruses had five and three amino acid mutations, respectively.

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The NS1-53 mutation in the DEN-2 PDK-53 vaccine virus is significant for the attenuated phenotype of this virus, because the NS1-53-Gly of the DEN-2 16681 virus is conserved in nearly all flaviviruses, including the tick-borne viruses, sequenced to date. The Mahidol DEN-4 vaccine virus also contains an amino acid mutation in the NS1 protein at position 253. This locus, which is a Gln-to-His mutation in DEN-4 PDK-48 vaccine virus is Gln in all four wild serotypes of dengue virus. This Gln residue is unique to the dengue viruses within the flavivirus genus. The NS1 protein is a glycoprotein that is secreted from flavivirus-infected cells. It is present on the surface of the infected cell and NS1-specific antibodies are present in the serum of virus-infected individuals. Protection of animals immunized with NS1 protein or passively with NS1-specific antibody has been reported. The NS1 protein appears to participate in early viral RNA replication.

The mutations that occurred in the NS2A, NS2B, NS4A, and NS4B proteins of the DEN-1, -2, -3 and -4 attenuated strains were all conservative in nature. The NS4A-75 and NS4A-95 mutations of DEN-2 and DEN-4 vaccine viruses, respectively, occurred at sites of amino acid conservation among dengue viruses, but not among flaviviruses in general.

The flaviviral NS3 protein possesses at least two recognized functions: the viral proteinase and RNA helicase/NTPase. The 698-aa long (DEN-2 virus) NS3 protein contains an amino-terminal serine protease domain (NS3-51-His, -75-Asp, -135-Ser catalytic triad) that is followed by sequence motifs for RNA helicase/NTPase functions (NS3-196-GAGKT (SEQ ID NO:147), -284-DEAH, -459-GRIGR (SEQ ID NO:148)). None of the mutations in the NS3 proteins of DEN-1, DEN-2, or DEN-3 virus occurred

within a recognized motif. The NS3-510 Tyr-to-Phe mutation in DEN-1 PDK-13 virus was conservative. Since the wild-type DEN-2, -3 and -4 viruses contain Phe at this position, it is unlikely that the Tyr-to-Phe mutation plays a role in the attenuation of DEN-1 virus. The NS3-182 Glu-to-Lys mutation in DEN-1 PDK-13 virus occurred at a position that is conserved as Asp or Glu in most mosquito-borne flaviviruses and it may play some role in attenuation. This mutation was located 15 amino acid residues upstream of the GAGKT (SEQ ID NO:147) helicase motif. As noted in previous reports, the NS3-250-Glu in DEN-2 16681 virus is conserved in all mosquito-borne flaviviruses except for yellow fever virus.

Method of Administration

The viral chimeras described herein are individually or jointly combined with a pharmaceutically acceptable carrier or vehicle for administration as an immunogen or vaccine to humans or animals. The terms "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" are used herein to mean any composition or compound including, but not limited to, water or saline, a gel, salve, solvent, diluent, fluid ointment base, liposome, micelle, giant micelle, and the like, which is suitable for use in contact with living animal or human tissue without causing adverse physiological responses, and which does not interact with the other components of the composition in a deleterious manner.

The immunogenic or vaccine formulations may be conveniently presented in viral PFU unit dosage form and prepared by using conventional pharmaceutical techniques. Such techniques include the step of bringing into association the active ingredient and the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers. Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions which may

include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water for injections, immediately prior to use.

- 5 Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets commonly used by one of ordinary skill in the art.

- Preferred unit dosage formulations are those containing a dose or unit, or an appropriate fraction thereof, of the administered ingredient. It should be understood that
- 10 in addition to the ingredients particularly mentioned above, the formulations of the present invention may include other agents commonly used by one of ordinary skill in the art.

- The immunogenic or vaccine composition may be administered through
- 15 different routes, such as oral or parenteral, including, but not limited to, buccal and sublingual, rectal, parenteral, aerosol, nasal, intramuscular, subcutaneous, intradermal, and topical. The composition may be administered in different forms, including, but not limited to, solutions, emulsions and suspensions, microspheres, particles, microparticles, nanoparticles and liposomes. It is expected that from about 1 to about 5
- 20 doses may be required per immunization regimen. Initial doses may range from about 100 to about 50,000 PFU, with a preferred dosage range of about 500 to about 20,000 PFU, a more preferred dosage range of from about 1000 to about 12,000 PFU and a most preferred dosage range of about 1000 to about 4000 PFU. Booster injections may range in dosage from about 100 to about 20,000 PFU, with a preferred dosage range of
- 25 about 500 to about 15,000, a more preferred dosage range of about 500 to about 10,000 PFU, and a most preferred dosage range of about 1000 to about 5000 PFU. For example, the volume of administration will vary depending on the route of administration. Intramuscular injections may range in volume from about 0.1 ml to 1.0 ml.

The composition may be stored at temperatures of from about -100°C to about 4°C. The composition may also be stored in a lyophilized state at different temperatures including room temperature. The composition may be sterilized through conventional means known to one of ordinary skill in the art. Such means include, but are not limited to, filtration. The composition may also be combined with bacteriostatic agents, such as thimerosal, to inhibit bacterial growth.

Administration Schedule

The immunogenic or vaccine composition described herein may be administered to humans, especially individuals traveling to regions where dengue virus infection is present, and also to inhabitants of those regions. The optimal time for administration of the composition is about one to three months before the initial infection. However, the composition may also be administered after initial infection to ameliorate disease progression, or after initial infection to treat the disease.

Adjuvants

A variety of adjuvants known to one of ordinary skill in the art may be administered in conjunction with the chimeric virus in the immunogen or vaccine composition of this invention. Such adjuvants include, but are not limited to, the following: polymers, co-polymers such as polyoxyethylene-polyoxypropylene copolymers, including block co-polymers, polymer P1005, Freund's complete adjuvant (for animals), Freund's incomplete adjuvant; sorbitan monooleate, squalene, CRL-8300 adjuvant, alum, QS 21, muramyl dipeptide, CpG oligonucleotide motifs and combinations of CpG oligonucleotide motifs, trehalose, bacterial extracts, including mycobacterial extracts, detoxified endotoxins, membrane lipids, or combinations thereof.

Nucleic Acid Sequences

Nucleic acid sequences of the DEN-1 16007 (SEQ ID NO:1), DEN-1 PDK-13 (SEQ ID NO:3), DEN-2 16681 (SEQ ID NO:13), DEN-2 PDK-53 (SEQ ID NO:15), DEN-3 16562 (SEQ ID NO:19), DEN-3 PGMK-30/FRhL-3 (SEQ ID NO:21), DEN-4 1036 (SEQ ID NO:23) and DEN-4 PDK-13 (SEQ ID NO:25) viruses are useful for designing nucleic acid probes and primers for the detection of dengue virus in a sample or specimen with high sensitivity and specificity. Probes or primers corresponding to each viral subtype can be used to detect the presence of DEN-1 virus, DEN-3 virus and DEN-4 virus, respectively, to detect dengue virus infection in general in the sample, to diagnose infection with dengue virus, to distinguish between the various dengue virus subtypes, to quantify the amount of dengue virus in the sample, or to monitor the progress of therapies used to treat a dengue virus infection. The nucleic acid and corresponding amino acid sequences are also useful as laboratory research tools to study the organisms and the diseases and to develop therapies and treatments for the diseases.

Nucleic acid probes selectively hybridize with nucleic acid molecules encoding the DEN-1, DEN-3 and DEN-4 viruses or complementary sequences thereof. By "selective" or "selectively" is meant a sequence which does not hybridize with other nucleic acids to prevent adequate detection of the dengue virus. Therefore, in the design of hybridizing nucleic acids, selectivity will depend upon the other components present in a sample. The hybridizing nucleic acid should have at least 70% complementarity with the segment of the nucleic acid to which it hybridizes. As used herein to describe nucleic acids, the term "selectively hybridizes" excludes the occasional randomly hybridizing nucleic acids, and thus, has the same meaning as "specifically hybridizing." The selectively hybridizing nucleic acid of this invention can have at least 70%, 80%, 85%, 90%, 95%, 97%, 98%, and 99% complementarity with the segment of the sequence to which it hybridizes, preferably 85% or more.

The present invention also contemplates sequences, probes and primers which selectively hybridize to the encoding nucleic acid or the complementary, or opposite, strand of the nucleic acid. Specific hybridization with nucleic acid can occur with minor modifications or substitutions in the nucleic acid, so long as functional species-specific hybridization capability is maintained. By "probe" is meant nucleic acid sequences that can be used as probes or primers for selective hybridization with complementary nucleic acid sequences for their detection or amplification, which probes can vary in length from about 5 to 100 nucleotides, or preferably from about 10 to 50 nucleotides, or most preferably about 18-24 nucleotides. Therefore, the terms "probe" or "probes" as used herein are defined to include "primers." Isolated nucleic acids are provided herein that selectively hybridize with the species-specific nucleic acids under stringent conditions and should have at least five nucleotides complementary to the sequence of interest as described in Molecular Cloning: A Laboratory Manual, 2nd Ed., Sambrook, Fritsch and Maniatis, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, (1989).

If used as primers, the composition preferably includes at least two nucleic acid molecules which hybridize to different regions of the target molecule so as to amplify a desired region. Depending on the length of the probe or primer, the target region can range between 70% complementary bases and full complementarity and still hybridize under stringent conditions. For example, for the purpose of detecting the presence of the dengue virus, the degree of complementarity between the hybridizing nucleic acid (probe or primer) and the sequence to which it hybridizes is at least enough to distinguish hybridization with a nucleic acid from other organisms.

The nucleic acid sequences encoding the DEN-1, DEN-3 or DEN-4 virus can be inserted into a vector, such as a plasmid, and recombinantly expressed in a living organism to produce recombinant dengue virus peptides and/or polypeptides.

Nucleic Acid Detection Methods

A rapid genetic test that is diagnostic for each of the vaccine viruses described herein is provided by the current invention. This embodiment of the invention enhances analyses of viruses isolated from the serum of vaccinated humans who developed a viremia, as well as enhancing characterization of viremia in nonhuman primates immunized with the Mahidol candidate vaccine viruses.

As provided in the complete nucleotide sequences of the wild-type parental and vaccine strains, and in the primer sequences provided in Table 16, the current invention comprises viruses specific probes and primers to detect one or more of the mutations that have been identified in the genome of each vaccine virus. Specific detection of two or more virus specific loci allows specific identification of the particular vaccine circulating in the serum of a vaccinee. Examples of such probes specifically designed to allow detection of each of the DEN-1, DEN-2, DEN-3 and DEN-4 vaccine virus-specific loci in a TaqMan assay are provided in Table 16.

These sequences include a diagnostic TaqMan probe that serves to report the detection of the cDNA amplicon amplified from the viral genomic RNA template by using a reverse-transcriptase/polymerase chain reaction (RT/PCR), as well as the forward (F in Table 16) and reverse (R in Table 16) amplimers that are designed to amplify the cDNA amplicon, as described below. In certain instances, one of the amplimers has been designed to contain a vaccine virus-specific mutation (underlined residues in Table 16) at the 3'-terminal end of the amplimer, which effectively makes the test even more specific for the vaccine strain because extension of the primer at the target site, and consequently amplification, will occur only if the viral RNA template contains that specific mutation. The probes and primers listed in Table 15 and Table 16 serve as examples of useful diagnostic sequences and are not intended to limit the design or scope of other probe and amplimer sequences that might be designed to detect the Mahidol vaccine virus-specific genetic mutations.

A recently developed, automated PCR-based nucleic acid sequence detection system is the TaqMan assay (Applied Biosystems), which is becoming widely used in diagnostic laboratories. The TaqMan assay is a highly specific and sensitive assay that permits automated, real time visualization and quantitation of PCR-generated
5 amplicons from a sample nucleic acid template. TaqMan can determine the presence or absence of a specific sequence. In this assay, a forward and a reverse primer are designed to anneal upstream and downstream of the target mutation site, respectively. A specific detector probe, which is designed to have a melting temperature of about 10°C higher than either of the primers and containing the vaccine virus-specific
10 nucleotide mutation or its complement (depending on the strand of RT/PCR amplicon that is being detected), constitutes the third primer component of this assay.

The probe is a fluorescent detector or reporter oligonucleotide that contains a 5'-reporter dye and a 3'-quencher dye. The 5' end of the nucleotide is linked to one of a
15 number of different fluorescent reporter dyes, such as FAM (6-carboxyfluorescein) or TET (tetrachloro-6-carboxyfluorescein). At the 3'-end of the probe, the quenching dye TAMRA (6-carboxytetramethylrhodamine) is attached via a linker. The quenching dye suppresses the fluorescence of the reporter dye in the intact probe, where both dyes are in close proximity. If the probe-specific target sequence is present in the RT/PCR
20 amplicon, the probe will anneal between the forward and reverse primer sites in the amplicon. If the probe hybridizes to the target sequence, the 5'-3' nuclease activity of AmpliTaq Gold DNA polymerase (Applied Biosystems) cleaves the probe between the reporter dye and the quencher dye. The polymerase will not digest free probe. Because the polymerase displaces the probe, polymerization and PCR amplification continue.
25 Once separated from the quencher dye, the reporter dye produces a fluorescence that is measured by the ABI PRISM Sequence Detection System. If the probe-specific target sequence is present in the amplicon, the level of fluorescence increases with, and is automatically measured at, each amplifying PCR cycle.

A probe designed to specifically detect a mutated locus in one of the Mahidol vaccine viral genomes will contain the vaccine-specific nucleotide in the middle of the probe. This probe will result in detectable fluorescence in the TaqMan assay if the viral RNA template is vaccine virus-specific. However, genomic RNA templates from wild-type DEN viruses will have decreased efficiency of probe hybridization because of the single nucleotide mismatch (in the case of the parental viruses DEN viruses) or possibly more than one mismatch (as may occur in other wild-type DEN viruses) and will not result in significant fluorescence. The DNA polymerase is more likely to displace a mismatched probe from the RT/PCR amplicon template than to cleave the mismatched probe to release the reporter dye (TaqMan Allelic Discrimination assay, Applied Biosystems).

A more recently developed strategy for diagnostic genetic testing makes use of molecular beacons (Tyagi and Kramer, *Nature Biotechnology* 14:303-308(1996)). The molecular beacon strategy also utilizes primers for RT/PCR amplification of amplicons, and detection of a specific sequence within the amplicon by a probe containing reporter and quencher dyes at the probe termini. In this assay, the probe forms a stem-loop structure. The 5'- and 3'- terminal reporter dye and quencher dye, respectively, are located at the termini of the short stem structure, which brings the quencher dye in close juxtaposition with the reporter dye. The stem-structure is melted during the denaturation step of the RT/PCR assay. If the target viral RNA contains the target sequence and is amplified by the forward and reverse amplimers, the opened loop of the probed hybridizes to the target sequence during the annealing step of the cycle. When the probe is annealed to either strand of the amplicon template, the quencher and reporter dyes are separated, and the fluorescence of the reporter dye is detected. This is a real-time identification and quantitation assay that is very similar to to the TaqMan assay. The molecular beacons assay employs quencher and reporter dyes that differ from those used in the TaqMan assay.

The present invention is further illustrated by the following non-limiting examples, which are not to be construed in any way as imposing limitations upon the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications, and equivalents thereof which, after reading the description herein, may suggest themselves to those skilled in the art without departing from the spirit of the present invention or the scope of the appended claims.

Example 1

Preparation of a Chimeric Dengue-1 Vaccine: PDK-53/Dengue-1

10

Viruses and cell cultures

Wild-type DEN-1 16007 and DEN-2 16681 viruses were available in the virus collection at the Centers for Disease Control and Prevention (Atlanta, GA). DEN-1 16007 virus was recovered from the serum of a patient with DHF/DSS in 1964 in Thailand. The virus was isolated following three passages in grivet monkey kidney BS-C-1 cells and one passage in LLC-MK₂ cells, passaged twice in *Toxorhynchites amboinensis* mosquitoes, and then passaged in primary dog kidney (PDK) cells at the Center for Vaccine Development, Mahidol University, Thailand, to derive the candidate DEN-1 PDK-13 vaccine virus (Yoksan et al., "Dengue virus vaccine development: study on biological markers of uncloned dengue 1-4 viruses serially passaged in primary kidney cells," pp. 35-38, In Arbovirus research in Australia. Proceedings of the Fourth Symposium. CSIRO/QIMR, Brisbane, Australia (1986); Bhamarapravati & Sutee, *Vaccine* 18: 44-47 (2000)). A single LLC-MK₂ passage of this candidate vaccine virus (lot March 10, 1989) was used, unless otherwise mentioned. Following the aforementioned mosquito passages, the 16007 virus was passaged once in LLC-MK₂ cells for use.

Viruses were grown in LLC-MK₂ and C6/36 cells in Dulbecco's modified minimal essential medium (DMEM) containing penicillin/streptomycin and 5% fetal bovine serum (FBS). Virus plaque titrations were performed in 6-well plates of

- confluent Vero or LLC-MK₂ cells as described previously (Miller et al., *Am. J. Trop. Med. & Hyg.* 35: 1302-1309 (1986)). The first 4-ml overlay medium -- containing 1% SeaKem LE agarose (FMC BioProducts, Rockland, Maine) in nutrient medium (0.165% lactalbumin hydrolysate [Difco Laboratories, Detroit, Mich.], 0.033% yeast extract [Difco], Earl's balanced salt solution, 25 mg/L of gentamycin sulfate [Bio Whittaker, Walkersville, Md.], 1.0 mg/L of amphotericin B [Fungizone, E. R. Squibb & Sons, Princeton, N.J.], and 2% FBS) -- was added after adsorption of the 200- μ l virus inoculum for 1.5 h at 37°C. Following incubation at 37°C for 7 days, a second 2-ml overlay containing an additional 80 μ g/ml of neutral red vital stain (GIBCO-BRL, Gaithersburg, Md.) was added. Plaques were counted 8 to 11 days after infection.

Construction of chimeric D2/1 infectious clones

pD2-16681-P48, pD2-PDK53-E48, pD2-PDK53-V48 vectors

- Three DEN-2 vectors were used for construction of the chimeric D2/1 clones.
- These were modified from the DEN-2 infectious clones reported by Kinney et al. (*Virology* 230: 300-308 (1997)). Clone pD2-16681-P48 was modified from pD2/IC-30P-A to contain cloning sites MluI and NgoMIV at nucleotide positions 451 and 2380, respectively. The same cloning sites were introduced into both DEN-2 PDK-53 virus-specific clones, pD2/IC-130Vx-4 and -130Vc-K, and the modified clones were designated as pD2-PDK53-E48 and pD2-PDK53-V48, respectively. Two cloning errors were found in the original pD2/IC-130Vx-4 and -130Vc-K at nt-6665 and nt-8840. These defects were corrected in pD2-PDK53-E48 and -V48. The introduced NgoMIV cloning site resulted in two nucleotide mutations (nt 2381 and 2382; TG to CC), which encoded a Val-to-Ala substitution at E-482. The nucleotide changes introduced at the MluI site were silent. The MluI site introduced at the C/prM junction was used to clone the prM-E genes of heterologous viruses.

Chimeric pD2/1-PP, -EP, -VP, -PV, -EV, and -VV

- Two intermediate DEN-2 clones, pD2I-P and pD2I-E, were constructed by deleting the HpaI (nt-2676) to XbaI (3' terminus of viral genomic cDNA) fragments of pD2-16681-P48 and pD2-PDK53-E48, respectively. These intermediate clones were
- 5 used to subclone DEN-1 virus-specific cDNA fragments. The cDNA fragments containing the C-prM-E genes of DEN-1 16007 or PDK-13 virus were amplified by reverse transcriptase - polymerase chain reaction (RT-PCR) from DEN-1 viral RNA with primers DEN-Bgl.5NC (5'-TAGAGAGCAGATCTCTG-3' (SEQ ID NO:31); conserved sequence in the 5'NCR of dengue viral genomes, underlined sequence is a
- 10 BglII site) and cD1-2394.Ngo: (5'-TGTGACCATGCGCGGCTGCGATGCACTCACCGA-3' (SEQ ID NO:32); underlined NgoMIV site followed by complementary sequence near the 3' end of the E gene of DEN-1 virus). Amplified fragments were cloned into the BglII-NgoMIV sites of the intermediate pD2I-P and pD2I-E clones. Intermediate, chimeric pD2/1 clones
- 15 were sequenced to verify the accuracy of the inserted DEN-1 virus-specific cDNA. Fragments excised from the intermediate pD2/1 clones with SstI (preceding the T7 promoter) and NgoMIV were cloned into the full genome-length DEN-2 vectors, pD2-16681-P48, pD2-PDK53-E48, and pD2-PDK53-V48. Six full genome-length chimeric pD2/1 plasmids were constructed by inserting the C-prM-E gene region of DEN-1
- 20 16007 or PDK-13 virus into these three vectors (FIG. 1). The plasmids were designated pD2/1-XY and their virus derivatives were designated DEN2/1-XY, where X = the infectious DEN-2 clone background (P = parental 16881 clone, E = PDK53-E variant, V = PDK53-V variant) and Y = DEN-1 virus-specific C-prM-E insert (P = parental 16007 strain, V = PDK-13 vaccine candidate). The PDK53-E backbone
- 25 contains three DEN-2 PDK-53 virus-specific amino acid mutations (NS1-53-Asp, NS2A-181-Phe and NS4A-75-Ala) as well as the 5'NC-57 mutation of PDK-53 virus. The PDK53-V backbone contains these same PDK-53 virus-specific loci plus the additional PDK-53 virus-specific NS3-250-Val locus.

Recovery of recombinant viruses

All recombinant plasmids were grown in *Escherichia coli* XL1-Blue cells. Recombinant viral RNA was transcribed and capped with the cap analog m⁷GpppA from 200-400 ng of XbaI-linearized cDNA, and transfected into 3-4 x 10⁶ LLC-MK₂ or BHK-21 cells by electroporation. Transfected cells were transferred to 75-cm² flasks in DMEM medium containing 10% FBS. Viral proteins expressed in the transfected cells were analyzed by indirect immunofluorescence assay (IFA). Virus-infected cells were fixed in ice-cold acetone for 30 min. DEN-1 and DEN-2 virus-specific monoclonal antibodies 1F1 and 3H5, respectively, were used in the assay, and binding was detected with fluorescein-labeled goat anti-mouse antibody. Viruses were harvested after 8 to 10 days, and were then passaged in LLC-MK₂ cells once (DEN-2-16681-P48, DEN-2-PDK53-E48 and -V48, DEN-2/1-PP, -EP, and -VP) or twice (DEN-2/1-PV, -EV, and -VV) to obtain working seeds. D2/1-EV and -VV viruses were passaged a third time in LLC-MK₂ cells to obtain higher viral titers required for challenge or immunization of mice.

Characterization of the replication phenotypes of chimeric viruses in cell cultures

Plaque sizes were measured 10 days after infection in LLC-MK₂ cells. Mean plaque diameters were calculated from 10 plaques for each virus. Viral growth curves were performed in 75-cm² flasks of LLC-MK₂ or C6/36 cells at approximately 0.001 multiplicity of infection (m.o.i.). After adsorption for 2 h, 30 ml of DMEM medium (for LLC-MK₂ cells) or overlay nutrient medium (for C6/36 cells) containing 5% FBS and penicillin/streptomycin was added, and the cultures were incubated in 5% CO₂ at 37°C or 29°C, respectively. Aliquots of culture medium were harvested at 48-h intervals for 12 days, adjusted to 12.5% FBS, and stored at -80°C prior to titration.

Temperature sensitivity was tested in LLC-MK₂ cells. Cells grown in two sets of 75-cm² flasks were infected and incubated as described for the growth curve study. One set of cultures was incubated for 8 days at 37°C, the other at 38.7°C. The ratio of virus titer at 38.7°C versus the titer at 37°C was calculated. Virus was designated as

temperature-sensitive if the virus titer at 38.7°C was reduced 60% or greater, relative its titer at 37°C.

Sequencing of viral cDNA

- 5 Viral RNA was extracted from virus seed or by using the QIAmp Viral RNA kit (Qiagen, Valencia, Calif.). DEN-1 virus-specific primers were based on the published data of the Singapore strain S275/90 (Fu et al., *Virology* 88: 953-958 (1992)). Five to 7 overlapping viral cDNA fragments were amplified by RT-PCR with the Titan One-Tube RT-PCR System (Roche Molecular Biochemicals, Indianapolis, Ind.). Both
- 10 strands of the cDNA amplicons were sequenced directly. For sequencing of the DEN-1 PDK-13 viral genome, template genomic RNA was extracted directly from a vial of the candidate DEN-1 PDK-13 vaccine (lot March 10, 1989). The 5'- and 3'- terminal sequences of the DEN-1 16007 and DEN-1 PDK-13 viral genomes were determined with the 5' RACE kit (GIBCO BRL) and by tailing the genomic RNA with poly(A).
- 15 Automated sequencing was performed as recommended on a PRISM 377 sequencer (Perkin-Elmer/Applied Biosystems, Foster City, Calif.).

Mouse studies

- Litters of newborn, 1-day-old outbred white ICR mice were inoculated
- 20 intracranially with 5,000 PFU of virus in a volume of 30 µl. They were observed daily for paralysis and death, and surviving mice were individually weighed once each week for 5 weeks.

- Neutralizing antibody responses were tested in 3-week-old ICR mice. They
- 25 were inoculated intraperitoneally with 10⁴ PFU of virus, and were boosted with the same amount of virus 3 weeks or 6 weeks later. Mice were bled 2 days prior to the boost and 3 weeks after boosting.

The ICR strain of inbred mice used above are not usually fatally susceptible to challenge with wild-type DEN-1 virus. Therefore, to fully test the ability of the DEN-2/1 viral chimera to induce an effective immune response, it was necessary to utilize inbred AG-129 mice, which lack receptors for both interferon alpha/beta and interferon gamma (Muller et al., *Science* 264:1918-1921 (1994)), as these mice have been found to be susceptible to intraperitoneal challenge with high doses of wild-type DEN-1 virus, strain Mochizuki. Therefore, 3.5-4.5-week-old inbred AG-129 mice were immunized intraperitoneally with 10^4 PFU of wild-type DEN-1 16007, Mahidol candidate vaccine DEN-1 PDK-13, chimeric DEN-2/1-EP or chimeric DEN-2/1-VP virus. These immunized mice were challenged intraperitoneally with a lethal dose of DEN-1 Mochizuki virus.

Neutralization Assays

Mouse serum samples were tested for neutralizing antibodies by serum- dilution plaque-reduction neutralization test (PRNT). Sixty PFU of DEN-1 16007 virus was incubated with serial 2-fold dilutions of heat-inactivated (56°C for 30 min) mouse serum specimens overnight at 4°C. The neutralizing antibody titer was identified as the highest serum dilution that reduced the number of virus plaques in the test by 50% or greater.

20

Results

To assess the potential of infectious cDNA clones derived from the two variants of DEN-2 16681 PDK-53 virus (PDK-53-E and PDK-53-V) to serve as vectors for vaccine development, we engineered chimeric DEN-2/DEN-1 cDNA clones (D2/1-EP, D2/1-VP, D2/1-EV, and D2/1-VV) containing the structural genes (C-prM-E) of wild-type DEN-1 16007 virus or its vaccine derivative, strain PDK-13, within the backbone of these two vectors (FIG. 1). Two other chimeric clones, D2/1-PP and D2/1-PV, containing the structural genes (C-prM-E) of DEN-1 16007 or PDK-13 virus in the backbone of wild-type DEN-2 16681 virus, were also constructed for comparison (FIG. 1). We sequenced the entire full-length genomic cDNA in all of the infectious clones.

A silent cDNA artifact was incorporated into the chimeric clones at nt-297 (T-to-C). A silent mutation at nt-1575 (T-to-C) was engineered into all of the chimeric clones to remove the natural XbaI site in the E gene of the DEN-1 virus.

- 5 Titers after transfection of LLC-MK₂ or BHK-21 cells were 10⁴-10⁶ PFU/ml for the chimeric viruses D2/1-PP, -EP, and -VP containing the C-prM-E of DEN-1 16007 virus. These titers increased to 10^{6.5}-10^{7.5} PFU/ml after a single passage in LLC-MK₂ cells, comparable to the titers obtained for their parental viruses. Lower titers of 10²-10⁴ PFU/ml were obtained in transfected cells for the chimeric DEN-2/1-PV, -EV, and -
- 10 VV viruses containing the C-prM-E of DEN-1 PDK-13 virus. D2/1-PV virus reached 10⁶ PFU/ml after 2 passages in LLC-MK₂ cells, whereas D2/1-EV and -VV viruses reached titers of 10^{3.3} - 10^{5.3} PFU/ml after two or three passages. Cells infected with any of the chimeric DEN-2/1 viruses were positive by IFA with monoclonal antibody 1F1 (specific for DEN-1 E protein) and negative with monoclonal antibody 3H5
- 15 (specific for DEN-2 E protein), indicating that appropriate DEN-1 E proteins were expressed by the chimeras. The DEN-2/1-PP, DEN-2/1-EP, and DEN-2/1-VP viral genomes were fully sequenced by directly analyzing overlapping RT-PCR fragments amplified from genomic viral RNA extracted from master seeds. All three genomes had the expected sequence.

20

Growth of the chimeric viruses in LLC-MK₂ and C6/36 cell cultures

- All of the chimeric DEN-2/1 viruses produced smaller plaques, relative to the 6.8 ±0.4-mm plaque of wild-type DEN-1 16007 virus in LLC-MK₂ cells (FIG. 2A). Both DEN-2/1-EP (3.1 ±0.3 mm) and -VP (2.8 ±0.3 mm) viral plaques were similar in
- 25 size to those of DEN-1 PDK-13 virus (2.9 ±0.3 mm). The chimeric viruses DEN-2/1-PV, DEN-2/1-EV, and DEN-2/1-VV containing the C-prM-E of DEN-1 PDK-13 virus formed tiny (1.3 ±0.3 mm) or pinpoint (<1 mm) plaques. The DEN-2 16681-P48 virus produced 3.5 ±0.3-mm plaques that were similar to plaques of wild-type DEN-2 16681 virus. The DEN-2 PDK53-V48 virus formed plaques that were smaller and fuzzier
- 30 than those of the DEN-2 PDK53-E48 virus. The 5.1 ±0.3-mm plaques of DEN-2/1-PP

virus were larger than those of the other chimeric viruses, but smaller than those of DEN-1 16007 virus.

Viruses were tested for temperature sensitivity in LLC-MK₂ cells. Temperature sensitivity was determined on day 8 or 10 after infection as indicated in FIG. 2B. Temperature sensitivity was based on the reduction of virus titers at 38.7°C from those at 37°C. Temperature sensitivity was calculated from measurements taken in at least 3 experiments.

The DEN-2 PDK53-V variant (D2-PDK53-V48) was more temperature sensitive than DEN-2 PDK53-E virus (D2-PDK53-E48) and DEN-2 16681 virus (DEN-2-16681-P48) was somewhat temperature sensitive (70-87% titer reduction at 38.7°C). Multiple temperature sensitivity tests for DEN-2-PDK53-E48 virus resulted in 83%-97% growth reduction. The titer of DEN-1 16007 virus was reduced by 40% or less at 38.7°C, making it the least-temperature sensitive virus in this study. All of the chimeric viruses were temperature sensitive relative to DEN-1 16007 virus, and were at least as temperature-sensitive as PDK-13.

All of the DEN-1, DEN-2, and chimeric D2/1 viruses reached peak titers between 8 and 10 days after infection in LLC-MK₂ cells (FIG. 2B). The clone-derived viruses DEN-2-16681-P48, DEN-2-PDK53-E48, and DEN-2-PDK53-V48 replicated to $10^{7.0}$ PFU/ml or greater, as did DEN-2 16681 and PDK-53 viruses. Although reaching similar peak titer, DEN-2-PDK53-V48 virus replicated slower than the DEN-2-PDK53-E48 virus during the first 4 days after infection. Chimeric DEN-2/1-PP, DEN-2/1-BP, DEN-2/1-VP, and DEN-2/1-PV viruses reached peak titers over $10^{6.7}$ PFU/ml, comparable to the peak titers of their parental DEN-1 and DEN-2 viruses. Chimeric DEN-2/1-EV and -VV viruses, which had peak titers of $10^{5.6}$ - $10^{5.9}$ PFU/ml or lower in several separate experiments, replicated less efficiently than the other viruses.

The PDK-13 virus-specific chimeras result in lower virus titers recovered from transfected cells, relative to the 16007 virus-specific chimeras. Previous experiences with DEN-2/DEN-1 and DEN-2/DEN-4 chimeras indicate that chimeric viruses which exhibit crippled replication during transfection and later develop high virus titers after passage in cell culture often accrued unexpected mutations. Viruses of increased replicative ability may arise through selection of subpopulations of virus variants, resulting from incorporation errors during *in vitro* transcription of cDNA. Chimeric viruses that replicate well in transfected cells were more genetically stable after passage in LLC-MK₂ cells. Efficient replication with minimal passage in mammalian cell culture may be an important criterion of genetic stability and suitability for an infectious clone-derived vaccine virus.

Viral growth curves in C6/36 cells were monitored following infection of C6/36 cells at an approximate multiplicity of 0.001 PFU/ml (FIG. 3). The three DEN-2 backbone viruses, DEN-2-16681-P48, DEN-2-PDK53-E48 and DEN-2-PDK53-V48, replicated like the original DEN-2 16681 virus and the two PDK-53 variants, respectively. Both DEN-2-PDK53-E48 and DEN-2-PDK53-V48 viruses replicated about 4000-fold less efficiently than the DEN-2-16681-P48, DEN-1 16007 and PDK-13 viruses in C6/36 cells. DEN-1 16007 and PDK-13 viruses replicated to high titers of $10^{8.7}$ and $10^{8.4}$ PFU/ml, respectively. The chimeric DEN-2/1-PP virus replicated to $10^{5.2}$ PFU/ml, which was equivalent to the peak titers of the two DEN-2-PDK53 variants. Replication of chimeric DEN-2/1-EP and DEN-2/1-VP viruses was very inefficient in C6/36 cells. These viruses reached peak titers of lower than 10^2 PFU/ml.

25 Neurovirulence in suckling mice

Groups of newborn to one-day-old ICR mice (n=16) were inoculated intracranially with 5000 PFU of virus. Wild-type DEN-2 16681 virus was 100% fatal with average survival time at 14.1 ± 1.6 days, while both clone-derived DEN-2-PDK53-E48 and DEN-2-PDK53-V48 viruses failed to kill any ICR mice. Unlike DEN-2 16681 virus, which typically kills 50% or greater of challenged mice, the wild-type

DEN-1 16007 virus caused only a single fatality (21 days after challenge) in the ICR mice. The DEN-1 PDK-13 virus did not kill any of the ICR mice. DEN-1 16007 virus-infected ICR mice had significantly lower mean body weights ($p < 0.00003$, Student's t test), relative to the control group inoculated with diluent, between 21-35 days after challenge. All of the ICR mouse groups challenged with five chimeric DEN-2/1 viruses (DEN-2/1-VV virus was not tested) had lower mean weights ($p < 0.02$) when compared to the control group, but their mean weights were significantly greater ($p < 0.004$) than the DEN-1 16007 group 28 days after infection. The mean body weights of ICR mouse groups challenged with 10^4 PFU of DEN-1 16007 or PDK-13 virus were nearly identical to those of the ICR mice challenged with 5000 PFU of DEN-1 16007 virus between 7-35 days after challenge.

Immunogenicity of chimeric DEN-2/1 viruses in mice

Outbred ICR Mice: To test the immunogenicity of the chimeric viruses, groups of 3-week-old ICR mice ($n=8$) were immunized intraperitoneally with 10^4 PFU of virus in Experiment 1 and Experiment 2 (Table 7). In Experiment 1, the mice were bled 20 days after primary immunization and then boosted 2 days later. In Experiment 2, the mice were bled 41 days after primary immunization and boosted 2 days later. Table 7 shows the reciprocal, 50% plaque-reduction endpoint PRNT titers of the pooled serum samples from each immunized group. The range of individual titers for the eight mice in many of the groups is also shown. In both experiments, the reciprocal titer of the pooled serum from 16007 virus-immunized mice was 80 before boost and 2560 after boost. In both experiments, mice immunized with chimeric DEN-2/1-PP, -EP, or DEN-2/1-VP viruses had a pooled serum titer that was at least as high as those of the 16007 virus-immunized groups before (reciprocal titers of 40-160) and after (reciprocal titers of 2560-5210) boost. The immune responses of the mice in these virus groups were nearly equivalent in both Experiment 1 and Experiment 2.

The PDK-13 virus and all three of the chimeras containing the PDK-13 structural genes induced minimal or low reciprocal PRNT titers of 10-20 against DEN-

1 16007 virus by 20 days after primary immunization in Experiment 1. A somewhat
higher reciprocal PRNT titer of 40 was elicited by each of these viruses by 41 days
after immunization in Experiment 2. The development of neutralizing antibodies was
slower and of lower magnitude following immunization with PDK-13, DEN-2/1-PV, -
5 EV, or -VV virus than with 16007, DEN-2/1-PP, -EP, or -VP virus in these mice. One
mouse in the DEN-2/1-PV group in Experiment 1 and one mouse in each of the DEN-
2/1-EV groups in both experiments failed to produce a detectable PRNT titer before
boost. Boosted titers were also higher for the PDK-13, DEN-2/1-PV, -EV, and -VV-
immunized groups in Experiment 2 (pooled reciprocal titers of 160-2560) than in
10 Experiment 1 (pooled reciprocal titers of 80). Except for the DEN-2/1-PV group in
Experiment 2, these boosted titers were lower than the boosted PRNT titers induced by
wild-type 16007 virus and chimeric DEN-2/1-PP, -EP, and -VP viruses containing the
structural genes of the wild-type DEN-1 16007 virus (Table 7). The high PRNT titer
obtained for the pooled serum of the mice boosted with DEN-2/1-PV virus resulted
15 from two mouse sera which had reciprocal titers of 2560 and 10,240. The remaining 6
mice in this group had reciprocal titers of 20 to 640, which were similar to the
individual titers of mice in the PDK-13, DEN-2/1-EV, and -VV groups. The PDK-13,
DEN-2/1-PV, DEN-2/1-EV, and DEN-2/1-VV viruses appeared to be less
immunogenic than the 16007, DEN-2/1-PP, -EP, and -VP viruses in these outbred
20 mice. Pooled serum samples from mice immunized with DEN-2-16681-P48, DEN-2-
PDK-53-E48, or DEN-2-PDK-53-V48 virus did not contain detectable cross
neutralizing antibody against DEN-1 16007 virus.

Inbred AG-129 Mice: To test the immunogenicity of the chimeric viruses,
25 groups of 3.5-4.5-week-old inbred AG-129 mice were immunized intraperitoneally
with 10^4 PFU of wild-type DEN-1 16007, Mahidol candidate vaccine DEN-1 PDK-13,
chimeric DEN-2/1-EP, or chimeric DEN-2/1-VP virus. At 26 days after primary
immunization, pooled sera from mice immunized with chimeric DEN-2/1-EP or DEN-
2/1-VP virus had reciprocal 70% serum dilution-plaque reduction neutralizing
30 antibody titers (PRNT₇₀) of 80-160. These titers were equivalent (within 2-fold) of the

neutralizing antibody response elicited by the candidate DEN-1 PDK-13 vaccine, but lower than the 640 titer elicited by the wild-type DEN-1 16007 virus. Control mice injected intraperitoneally with phosphate buffered saline had titers of less than 10. All mice were challenged intraperitoneally with 10^7 PFU of wild-type, virulent DEN-1 virus, strain Mochizuki, at 28 days after primary immunization. All eleven of the control, non-immunized mice died within 21 days (average survival time of 11.5 ± 4.2 days [mean \pm standard deviation]) after challenge, whereas all of the DEN-1 (16007, PDK-13, DEN-2/1-EP, DEN-2/1-VP) virus-immunized mice survived challenge with DEN-1 Mochizuki virus. At 34 days after challenge with DEN-1 Mochizuki, all of the virus-immunized mice had reciprocal PRNT₇₀ titers of 1280-2560. The chimeric DEN-2/1-EP and DEN-2/1-VP viruses were highly immunogenic and protective for AG-129 mice.

Nucleotide sequence analyses of DEN-1 16007 and PDK-13 viral genomes

We sequenced the genomes of wild-type DEN-1 16007 virus (GenBank accession number AF180817) and its PDK-13 vaccine derivative (accession number AF180818). There were 14 nucleotide and 8 encoded amino acid differences between 16007 and PDK-13 viruses (Table 2). Silent mutations occurred at genome nucleotide positions 1567, 2695, 2782, 7330, and 9445 in the E, NS1, NS4B, and NS5 genes. Unlike the candidate DEN-2 PDK-53 vaccine virus, which has no amino acid mutations in the E protein, the DEN-1 PDK-13 virus had five amino acid mutations in E, including E-130 Val-to-Ala, E-203 Glu-to-Lys, E-204 Arg-to-Lys, E-225 Ser-to-Leu, and E-447 Met-to-Val. Amino acid mutations in the nonstructural genes included NS3-182 Glu-to-Lys, NS3-510 Tyr-to-Phe, and NS4A-144 Met-to-Val. The PDK-13 virus-specific E-477-Val was incorporated into all of the chimeric constructs.

Immunization of monkeys with chimeric DEN-2/1 viruses

The immunogenicity of the chimeric DEN-2/1-EP and DEN-2/1-VP viruses in adult crab-eating monkeys (*Macaca fascicularis*) was tested. Immunization of monkeys was accomplished by means of subcutaneous injection with 10^6 PFU of

chimeric DEN-2/1-EP or DEN-2/1-VP virus. Sera obtained from the immunized monkeys were analyzed for the presence of viremia by direct plaque assay of serum aliquots in LLC-MK₂ cell monolayers maintained under agarose overlay in 6-well plates, and by inoculation of serum aliquots into cultures of LLC-MK2 cells maintained in liquid medium. No infectious virus was identified in any of the monkey sera by either of these two classical assay methods. By these two virus assays, no viremia was detectable following immunization with either chimeric DEN-2/1-EP or DEN-2/1-VP virus. Monkey sera were tested for DEN-1 virus-specific neutralizing antibodies. At 30 days after primary immunization, sera from three individual monkeys immunized with chimeric DEN-2/1-EP virus had reciprocal 50% serum dilution-plaque reduction neutralizing antibody titers (PRNT₅₀) of 80, 160 and 1280. Sera from three individual monkeys immunized with chimeric DEN-2/1-VP had reciprocal PRNT₅₀ titers of 160, 160 and 640. Monkeys injected with diluent as a control for the experiment had reciprocal PRNT₅₀ titers of less than 10, as did all of the monkeys just prior to immunization. The chimeric DEN-2/1-EP and -VP viruses elicited DEN-1 virus-specific neutralizing antibodies in non-human primates.

Example 2

Construction Of Chimeric DEN-2/3 Infectious Clones

An in vitro ligation strategy was used for the full genome-length DEN-2/3 infectious clones.

(i) 5'-end DEN-2/3 intermediate clones: pD2I/D3-P1-Asc and pD2I/D3-E1-Asc

Intermediate DEN-2 clones, pD2I-P and pD2I-E were used to subclone the DEN-3 16562 virus-specific cDNA fragment. The cDNA fragment containing the prM-E genes of wild-type DEN-3 16562 virus was amplified by reverse transcriptase - polymerase chain reaction (RT-PCR) from DEN-3 viral RNA with primers D3-435.Mlu:

(5'-TGCTGGCCACTTAACTACGCGTGATGGAGAGCCGCGCA-3' (SEQ ID NO:33); underlined MluI site followed by DEN-3 virus sequence near the 5' end of the

prM gene) and cD3-2394.Ngo:

(5'-TGTAATGATGCCGGCCGCGATGCATGAAAATGA-3' (SEQ ID NO:34);

underlined NgoMIV site followed by complementary sequence near the 3' end of the E gene of DEN-3 virus). The MluI site contained a silent mutation for DEN-2 virus at

- 5 amino acid prM-5-Thr. This position is Ser in DEN-3 virus, but Thr in chimeric DEN-2/3 virus. The NgoMIV site resulted in a Val-to-Ala substitution at E-482 of DEN-2 virus, and an Ile-to-Ala substitution at E-480 of DEN-3 virus. The amplified fragment was cloned into the MluI-NgoMIV sites of the intermediate pD2I-P and pD2I-E clones. A restriction site, AscI, was introduced downstream of the NgoMIV site by site-
- 10 directed mutagenesis to facilitate *in vitro* ligation. This unique AscI site was only 16 nts downstream from the NgoMIV site and was excised prior to *in vitro* ligation of the full-length DEN-2/3 clones. An additional mutagenesis at nt 1970 (A-to-T) which changed amino acid E-345 from His to Leu, was introduced to permit derivation of viable chimeric viruses in LLC-MK₂ cells, as explained below. These intermediate chimeric
- 15 DEN-2/3 clones, pD2I/D3-P-Asc and pD2I/D3-E-Asc, were sequenced to verify the accuracy of the inserted DEN-3 virus-specific cDNA. A silent mutation was incorporated at nt 552 (C-to-T) in both intermediate chimeric clones.

(ii) 3'-end DEN-2 intermediate clones: pD2-Pm^b-Asc, pD2-Em^b-Asc, and pD2-

- 20 Vm^b-Asc

Intermediate DEN-2 clones containing the truncated DEN-2 virus-specific cDNA sequence from nt 2203-10723 (3'-end) of DEN-2 16681, PDK53-E, or PDK-53-V virus were obtained by deletion of the 5' end (including T7 promoter sequence and DEN-2 nts 1-2202) of the virus specific cDNA in the full-length clones, pD2-16681-P48, pD2-PDK53-E48, and pD2-PDK53-V48, respectively. An AscI site was also

- 25 introduced at nt 2358 (22 nts upstream of the NgoMIV site) to facilitate the *in vitro* ligation. This AscI site was excised prior to performing the *in vitro* ligation of the full genome-length, chimeric DEN-2/3 infectious clones.

(iii) Full-length chimeric DEN-2/3 cDNA: DEN-2/3-PP1, DEN-2/3-EP1, and DEN-2/3-VP1

Three to ten mg of the 5'-end pD2I/D3 and 3'-end D2 intermediate clones were digested by AscI, treated with calf intestine phosphatase (CIP), and then digested with
 5 NgoMIV. The excised small AscI-NgoMIV fragments were removed by passing the digested DNA through Qiagen PCR-purification spin columns. The large 5'- and 3'-end, linearized intermediate clones were then ligated together (5' : 3' = 1:3 molar ratio) to obtain full genome-length DEN-2/3-PP1 (pD2I/D3-P1-Asc ligated with pD2- Pm^b-Asc), DEN-2/3-EP1 (pD2I/D3-E1-Asc ligated with pD2-Em^b-Asc), and DEN-2/3-
 10 VP1 (pD2I/D3- E1-Asc ligated with pD2-Vm^b-Asc). These ligated DNAs were then cut with XbaI to produce the linearized 3'-end of the viral cDNA required for transcription of the recombinant viral RNA.

Recovery of chimeric DEN-2/3 viruses

15 Recombinant viral RNA was transcribed from XbaI- linearized cDNA and capped with the cap analog m⁷GpppA. LLC-MK₂ or BHK-21 cells (3- 5 x 10⁶ cells) were transfected by electroporation as described by Kinney et al. (*J. Virol* 230: 300-308 (1997)). Transfected cells were transferred to 75-cm² flasks in DMEM medium containing 10% FBS. Viral proteins expressed in the transfected cells were analyzed
 20 by indirect immunofluorescence assay (IFA). Virus-infected cells were fixed in ice-cold acetone for 30 min. DEN-3 and DEN-2 virus-specific monoclonal antibodies 8A1 and 3H5, respectively, were used in the assay, and binding was detected with fluorescein-labeled goat anti-mouse antibody. Viruses were harvested after 5 to 11 days, and were then passaged in LLC-MK₂ cells once to obtain working seeds. Viral
 25 genomes extracted from these seeds were sequenced to confirm the genotypes of the progeny viruses. An earlier strategy using 5'-end D2I/D3 intermediate clones containing authentic DEN-3 16562 prM-E genes resulted in mutations at several different positions in the genomes of the viruses recovered from transfected LLC-MK₂ or BHK-21 cells and passaged once in LLC- MK₂ cells. A mutation at nt 1970 from A
 30 to T, which changed amino acid E-345 from His to Leu, was found in seven of nine

independently recovered recombinant viruses. It was obvious that the original DEN-2/3 chimeric viruses were unstable in LLC-MK₂ and/or BHK-21 cells. The single mutation at E-345 was the only mutation that occurred in the genomes of three recovered viruses, indicating that this mutation might help to stabilize the viruses in culture. We introduced this mutation in all the infectious DEN-2/3 clones and recombinant viruses recovered from such mutagenized clones proved to be stable in cell culture.

Example 3

Construction Of Chimeric DEN-2/4 Infectious Clones

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pD2-16681-P48, pD2-PDK53-E48, pD2-PDK53-V48 vectors

The three DEN-2 backbone vectors used for construction of the chimeric DEN-2/4 clones were modified as described above. The DEN-2 infectious clones have been previously reported in Kinney et al., 1997. Clone pD2-16681-P48 was modified from pD2/IC-30P-A to contain cloning sites MluI and NgoMIV at nucleotide positions 451 and 2380, respectively. The same cloning sites were introduced into both DEN-2 PDK-53 virus-specific clones, pD2/IC-130Vx-4 and -130Vc-K, and the modified clones were designated as pD2-PDK53-E48 and pD2-PDK53-V48, respectively. Two cloning errors were found in the original pD2/IC-130Vx-4 and -130Vc-K at nt-6665 and nt-8840. These defects were corrected in pD2-PDK53-E48 and -V48. The introduced NgoMIV cloning site resulted in two nucleotide mutations (nt 2381 and 2382; TG to CC), which encoded a Val-to-Ala substitution at E-482 of DEN-2 virus. The nucleotide changes introduced at the MluI site were silent for DEN-2 virus and chimeric DEN-2/4 viruses. The MluI site (near the C/prM junction) and NgoMIV site (close to E/NS1 junction) were used to clone the prM-E genes of heterologous viruses.

Chimeric pDEN-2/4-PP1, -EP1, and -VP1

Two intermediate DEN-2 clones, pD2I-P and pD2I-E, were constructed by deleting the HpaI (nt-2676) to XbaI (3' terminus of viral genomic cDNA) fragments of pD2-16681-P48 and pD2-PDK53-E48, respectively. These intermediate clones were

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used to subclone DEN-4 1036 virus-specific cDNA fragments. The cDNA fragment containing the prM-E genes of DEN-4 1036 virus was amplified by reverse transcriptase - polymerase chain reaction (RT-PCR) from DEN-4 viral RNA with primers D4-453Mlu:

- 5 (5'-GGCGTTTCACTTGTCAACGCGTGATGGCGAACCCCTCA-3' (SEQ ID NO:35); underlined MluI site followed by sequence near the 5' end of the DEN-4 1036 viral genome) and cD4-2394.Ngo:
(5'-AGTGATTCCGCCGGCAGCTATGCACGTCATAGCCAT-3' (SEQ ID NO:36); underlined NgoMIV site followed by complementary sequence near the 3' end of the E gene of DEN-4 virus). Amplified fragments were cloned into the MluI-NgoMIV sites of the intermediate pD2I-P and pD2I-E clones. Intermediate, chimeric DEN-2/4 clones were sequenced to verify the accuracy of the inserted DEN-4 virus-specific cDNA. A silent mutation was incorporated at nt 1401 (A-to-G) in both intermediate clones. Fragments excised from the DEN-2/IC-P48, -VE48, and -VV48 clones with NgoMIV and ScaI (downstream of DEN-2 cDNA sequence in these plasmids) were cloned into NgoMIV/ScaI-cut chimeric D2/4 intermediate clones to obtain the full-length chimeric D2/4-PP, -EP, and -VP clones. However, transcribed RNA from these chimeric clones only produced viable DEN-2/4 chimeric viruses in transfected C6/36 cells, but not in transfected LLC-MK₂ cells. After passaging the chimeric viruses in C6/36 cells one more time to obtain higher titers, these viruses were passaged in LLC-MK₂ cells five times to obtain stable chimeric DEN-2/4 viruses which replicated efficiently in LLC-MK₂ cells. Titers of the virus seeds increased from 200 PFU/ml at the first LLC-MK₂ cell passage to over 10⁶ PFU/ml at the fifth LLC-MK₂ cell passage.

- 25 The genomes of viruses from the first, second, third and fifth LLC-MK₂ cell passages of the chimeric DEN-2/4-PP viruses were sequenced. Four mutations, DEN-2 virus-specific, C-100 (Arg-to-Ser), DEN-4 virus-specific E-364 (Ala to-Ala/Val mix), DEN-4 virus-specific E-447 (Met-to-Leu) and DEN-2 virus-specific NS4B-239 (Ile-to-Leu) were identified (amino acid positions based on chimeric DEN-2/4 virus sequences). The three mutations located in the structural genes (C and E) were
- 30

introduced into the chimeric DEN-2/4-PP, -EP, and -VP infectious cDNA clones to obtain DEN-2/4-PP1, -EP1, and -VP1 clones, respectively. All three of these chimeric DEN-2/4 clones produced viable, high-titered chimeric viruses in LLC-MK₂ cells immediately after transfection indicating that these three mutations helped the viruses to replicate in LLC-MK₂ cells. Chimeric DEN-2/4 clones were also mutagenized to contain different combinations of the four mutations to determine which mutations are needed for replication efficiency of the chimeric DEN-2/4 viruses in LLC-MK₂ cells. The DEN-4 E-447 (Met-to-Leu) mutation alone or together with the DEN-4 E-364 mutation, in combination with the DEN-2 C-100 (Arg-to-Ser) mutation was adequate to allow derivation of DEN-2/4 virus in LLC-MK₂ cells.

Recovery of recombinant viruses.

Recombinant plasmids pD2/4-PP1, -EP1, and -VP1 all were grown in *Escherichia coli* XL1-Blue cells. Recombinant viral RNA was transcribed and capped with the cap analog m⁷GpppA from 200-400 ng of XbaI-linearized cDNA, and transfected into 3-5.10⁶ LLC-MK₂ cells. Transfected cells were transferred to 75-cm² flasks in DMEM medium containing 10% FBS. Viral proteins expressed in the transfected cells were analyzed by indirect immunofluorescence assay (IFA). Virus-infected cells were fixed in ice-cold acetone for 30 min. DEN-4 and DEN-2 virus-specific monoclonal antibodies 1H10 and 3H5, respectively, were used in the assay, and binding was detected with fluorescein-labeled goat anti-mouse antibody. Viruses were harvested after 8 to 10 days, and were then passaged in LLC-MK₂ cells once to obtain working seeds. The genomes of all these three working seeds were fully sequenced, and all the chimeric DEN-2/4 viral genomes contained the expected sequences. The nucleotide and amino acid sequences for the DEN 2/4 chimera are provided herein at SEQ ID NO:13 and SEQ ID NO:14, respectively.

Example 4***Characterization of DEN-2/3 and DEN-2/4 Chimeric Viruses***

The viable, infectious chimeric DEN-2/3 and DEN-2/4 viruses, which express
5 the prM/E gene region of wild-type DEN-3 16562 or wild-type DEN-4 1036 virus,
respectively, expressed appropriate DEN-3 or DEN-4 virus-specific envelope protein
(E) epitopes, as analyzed by indirect immunofluorescence of virus-infected LLC-MK₂
cells with virus-specific anti-E monoclonal antibodies. These chimeric viruses, as well
as chimeric DEN-2/1 virus, also expressed appropriate DEN serotype-specific
10 neutralization epitopes when tested against standard polyvalent mouse ascitic fluids or
monoclonal antibodies in serum dilution-plaque reduction neutralization tests (Table 8).
The chimeric DEN-2/1-EP, DEN-2/3-EP1, and DEN-2/4-EP1 viruses were neutralized
by these standard DEN virus-specific antibodies to reciprocal PRNT₅₀ titers that were at
least as high as those that occurred for wild-type DEN-1, DEN-3, and DEN-4 viruses,
15 respectively (Table 8). These neutralization data indicated that the chimeric DEN-2/1,
DEN-2/3, and DEN-2/4 viruses expressed appropriate DEN serotype-specific
neutralization epitopes of DEN-1, DEN-3, and DEN-4 viruses, respectively.

20 Replication in LLC-MK2 cells

The replication and temperature sensitivity of DEN-2/3 chimeras in LLC-MK2
cells was monitored as the replication and temperature sensitivity of DEN-2/1 chimeras
was examined in Example 1. The chimeric DEN-2/3-PP1, -EP1, and -VP1 viruses and
chimeric DEN-2/4-PP1, -EP1, and -VP1 viruses, which expressed the prM/E gene
25 region of DEN-3 16562 virus or DEN-4 1036 virus in the genetic background of DEN-
2 16681 (-PP1), DEN-2 PDK-53-E variant (-EP1), or the DEN-2 PDK-53-V variant (-
VP1), respectively, all replicated to high peak titers of at least 10^{6.3} PFU/ml in LLC-
MK₂ cells. As defined in terms of the reduction of virus titers at 38.7°C versus those at
37°C (-, +, 2+, 3+ indicate titer reduction of less than or equal to 60%, 61-90%, 91-
30 99%, >99%, respectively, calculated from at least 3 experiments). Chimeric DEN-2/3-

PP1 and DEN-2/4-PP1 viruses exhibited either borderline temperature sensitivity (DEN-2/3-PP1) or no temperature sensitivity (DEN-2/4-PP1). The chimeric DEN-2/3-EP1 and -VP1, as well as the chimeric DEN-2/4-EP1 and -VP1 viruses, all of which were constructed in the genetic background of the DEN-2 PD-53-E or -V variant, retained the temperature-sensitive phenotypes that were exhibited by the two PDK-53 variant viruses (DEN-2-PDK53-E48 and -V48 viruses, respectively). The chimeras constructed in the background of the PDK-53-V variant exhibited a higher degree of temperature sensitivity than did those constructed in the background of the PDK-53-E variant.

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Plaque sizes in LLC-MK2 cells

The plaque size resulting from inoculation of LLC-MK2 cells placed under agarose overlay, used as a biological marker to determine attenuation as described in Example 1, was also examined for the chimeric DEN-2/3 and DEN-2/4 viruses.

15 Average plaque size in mm follows each virus or chimera in brackets: DEN-3-16562 (6.6), DEN-2/3-PP1 (5.4), DEN-2/3-EP1 (4.5), DEN-2/3-VP1 (2.3), DEN-4-1036 (8.6), DEN-2/4-PP1 (3), DEN-2/4-EP1 (1.5), DEN-2/4-VP1 (1.2), DEN-2-16681-P48 (4.2), DEN-2-PDK53-E48 (2.5) and DEN-2-PDK-53-V48 (1.8).

20 The plaque sizes of the DEN-2/3-PP1 and DEN-2/4-PP1 viruses exhibited mean plaque diameters that were larger than those of the DEN-2 16681 or PDK-53 virus (as described in Example 1), but smaller than those of wild-type DEN-3 16562 and DEN-4 1036 viruses, respectively. This indicates that structural genes from the donor DEN-3 and DEN-4 viruses and capsid and/or nonstructural gene regions in the recipient genetic background of DEN-2 16681 virus both affected plaque size. The chimeric DEN-2/3-EP1 and -VP1 and DEN-2/4-EP1 and -VP1 viruses exhibited significant reductions in plaque size, relative to wild-type DEN-3 16562 and DEN-4 1036 viruses, respectively. The DEN-2 PDK-53 background-specific effect on plaque size may result from synergistic interaction of the mutations at the NS1-53 and NS3-250 loci of DEN-2

25 background of DEN-2 16681 virus both affected plaque size. The chimeric DEN-2/3-EP1 and -VP1 and DEN-2/4-EP1 and -VP1 viruses exhibited significant reductions in plaque size, relative to wild-type DEN-3 16562 and DEN-4 1036 viruses, respectively. The DEN-2 PDK-53 background-specific effect on plaque size may result from synergistic interaction of the mutations at the NS1-53 and NS3-250 loci of DEN-2

30 PDK-53 virus. Consequently, -VP1 chimeras exhibited greater reductions in plaque

size than did the -EP1 chimeras. The chimeric DEN-2/1, DEN-2/3, and DEN-2/4 viruses constructed in the genetic background of the candidate DEN-2 PDK-53 vaccine virus retained the phenotype of decreased plaque size as exhibited by DEN-2 PDK-53 virus.

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Replication in C6/36 cells

The ability of the viruses to replicate in mosquito C6/36 cell culture, used as a biological marker to determine attenuation as described in Example 1, was also examined for the chimeric DEN-2/3 and DEN-2/4 viruses. Average peak titers in units of Log₁₀ PFU/ml follow each virus or chimera in brackets; D3-16562 (7.3), DEN-2/3-PP1 (7.6), DEN-2/3-EP1 (5.2), DEN-2/3-VP1 (5.7), D4-1036 (8.7), DEN-2/4-PP1 (7.8), DEN-2/4-EP1 (4.5), DEN-2/4-VP1 (4.4), DEN-2-16681-P48 (8.3), DEN-2-PDK53-E48 (5.4) and DEN-2-PDK-53-V48 (5).

- 15 Both of the Mahidol candidate DEN-2 PDK-53 variants exhibit decreased replication efficiency, relative to wild-type DEN-2 16681 virus, in mosquito C6/36 cell culture (DEN-2-PDK-53-E48 and -V48 versus DEN-2-16681-P48 virus). The decreased replication ability in C6/36 cells has been attributed to the mutations at the two 5'-NC-57 and NS1-53 loci in the DEN-2 PDK-53 virus; consistent with this view,
- 20 both variants replicated to equivalently reduced peak titers in these cells. This crippled replication phenotype in C6/36 cells was retained in the chimeric DEN-2/3-EP1 and -VP1 and DEN-2/4-EP1 and -VP1 viruses, all of which replicated to lower peak titers than did the wild-type DEN-3 16562 or DEN-4 1036 virus, respectively. The chimeric DEN-2/3-PP1 and DEN-2/4-PP1 viruses, constructed in the genetic background of
- 25 wild-type DEN-2 16681 virus, replicated to essentially the same extent (DEN-2/3-PP1) as or somewhat lower (DEN-2/4-PP1) than the wild-type DEN-3 16562 and DEN-4 1036 viruses, respectively. These results indicate that the replication-crippling effect of the 5'-NC-57 and NS1-53 loci in the DEN-2 PDK-53 virus-specific background was preserved in those chimeric viruses that were constructed within the DEN-2 PDK-53
- 30 genetic background.

Neurovirulence for newborn mice

Newborn, outbred, white ICR mice (n=16 for each group) were challenged intracranially with 10^4 PFU of wild-type DEN-3 and DEN-4 viruses, Mahidol candidate vaccine DEN-3 and DEN-4 viruses, chimeric DEN-2/3-PP1, -EP1, -VP1 viruses, and chimeric DEN-2/4-PP1, -EP1, and -VP1 viruses (Table 9). The wild-type DEN-3 16562 and DEN-4 1036 viruses, which reliably caused 100% fatality in newborn mice, constituted a more sensitive model for attenuation of viral neurovirulence than does the DEN-2 16681 challenge model, which results in 50-100% fatality in newborn mice challenged with this virus. Interestingly, the Mahidol candidate DEN-4 PDK-48 vaccine virus also resulted in 100% fatality in challenged mice, although the average survival time of these mice was about two days longer than for mice challenged intracranially with wild-type DEN-4 1036 virus (Table 9). Like the DEN-2 PDK-53 vaccine virus and both of its variant populations, the chimeric DEN-2/3-EP1 and -VP1 and chimeric DEN-2/4-EP1 and -VP1 viruses were attenuated (no fatalities) for newborn mice. This attenuation may be attributable, at least in part, to the attenuated DEN-2 PDK-53 genetic background of these chimeric viruses, because the chimeric DEN-2/4-PP1 virus exhibited significant neurovirulence (62.5% mortality) in these mice. This latter chimera was constructed in the genetic background of wild-type DEN-2 16681 virus.

20

Immunization of AG-129 mice with chimeric DEN-2/3 and DEN-2/4 viruses

Inbred AG-129 mice were immunized intraperitoneally with 10^5 PFU of wild-type or Mahidol vaccine candidate DEN-3 or DEN-4 virus or with 10^5 PFU of chimeric DEN-2/3-EP1 or DEN-2/4-EP1 virus (Table 10). The chimeric DEN-2/3-EP1 virus elicited reciprocal PRNT₅₀ titers of 80-320 at 4-6 weeks after primary immunization. These titers were essentially equivalent to those elicited by the Mahidol DEN-3 vaccine

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virus (strain PGMK-30/FRhL-3). However, the chimeric DEN-2/4-EP1 virus elicited neutralizing antibody titer of 20-40, which was lower than the 80-320 titer elicited by the Mahidol vaccine candidate DEN-4 PDK-48 vaccine virus. Nevertheless, both chimeric DEN-2/3 and DEN-2/4 viruses elicited neutralizing antibody responses in
5 AG-129 mice.

Example 5

Attenuation of a Dengue-2 Vaccine Virus: Strain 16681 (PDK-53)

Viruses and cell cultures

10 The parental DEN-2 16681 virus, several intermediate PDK passages (PDK-5, -10, -14, -35, and -45) of 16681 virus, recombinant 16681/PDK-53 viruses, and the genetically characterized LLC-MK₂-1 passage of the candidate PDK-53 vaccine virus were investigated.

15 Cell cultures of BHK-21 (clone 15), LLC-MK₂, Vero, and C6/36 were grown in Dulbecco's modified minimal essential medium (DMEM) supplemented with 10% heat-inactivated (56°C for 30 min) fetal bovine serum (FBS; HyClone Laboratories, Inc., Logan, Utah), 3.7 g/L of sodium bicarbonate (GIBCO-BRL, Life Technologies, Gaithersburg, Md.), 100 units/ml of penicillin G, and 100 mg/ml of streptomycin
20 sulfate (GIBCO-BRL).

Plaque titrations were performed in confluent monolayers of Vero cells in plastic 6-well plates as described previously (Miller et al., *Am. J. Trop. Med. & Hyg.* 35: 1302-1309 (1986)). A 200- μ l inoculum of virus was adsorbed for 1.5 h at 37°C,
25 followed by the addition of 4 ml of agarose overlay medium containing 1% SeaKem LE agarose (FMC BioProducts, Rockland, Md.) in nutrient medium (0.165 % lactalbumin hydrolysate [Difco Laboratories, Detroit, Mich.], 0.033% yeast extract [Difco], Earl's balanced salt solution, 25 mg/L of gentamicin sulfate [Bio Whittaker, Walkersville, Md.], 1.0 mg/L of amphotericin B [Fungizone®, E. R. Squibb & Sons, Princeton, N.J.], and 2% FBS). Following incubation at 37°C for 7 days, a second 2-ml

agarose overlay containing 80 µg/ml of neutral red vital stain (GIBCO-BRL) was added.

Construction of recombinant DEN-2 16681/PDK-53 viruses

- 5 During the genetic validation of clone-derived DEN-2 viruses in the present study, two cDNA cloning errors were discovered, nt-6665 A-to-G (NS4A-97 Tyr-to-Cys) and nt-8840 A-to-G (NS5-424 Glu-to-Gly), in the previously reported PDK-53 virus-specific pD2/IC-130Vc-K (NS3-250-Val variant) clone (Kinney et al., Virology 230: 300-308 (1997)). These defects were corrected in a newly derived PDK-53 virus-
10 specific (NS3-250-Val variant) clone, pD2/IC-VV45R.

In preliminary studies, recombinant 16681/PDK-53 viruses containing PDK-53 virus-specific gene regions within the genetic background of 16681 virus were used to investigate the genetic loci involved in the attenuation markers of PDK-53 virus.

- 15 Analyses of these viruses indicated that the PDK-53 mutation at nt-57 in the 5'NC region and the amino acid mutations at NS1-53 (analyzed in a linked manner with the NS2A-181 mutation) and NS3-250 were the determinants of the PDK-53 virus-specific phenotype. The prM-29 mutation has little effect on virulence. Based upon sequence analysis and comparison, the 5'NC, NS1 and NS3 mutations were subjected to further
20 mutational analysis. The 5'NC mutation occurred in a possible stem structure. The NS1 and NS3 mutations both occurred at loci conserved in some flaviviruses. 14 recombinant pD2/IC- 16681/PDK-53 plasmids were constructed by exchanging cDNA fragments between pD2/IC-30P-A (16681 clone) and pD2/IC-VV45R (PDK-53 clone) at restriction enzyme sites SstI (preceding the T7 promoter), SalI (nt-165), SphI (nt-
25 1380), SpeI (nt-2370 and nt-3579), KpnI (nt-4493), XhoI (nt-5426), and XbaI (3' end of the clone). All recombinant plasmids were grown in *Escherichia coli*, strain XLI-blue, and were linearized at the unique XbaI site engineered at the 3' terminus of the cDNA. BHK-21 cells were transfected with transcribed viral RNA by the method of Liljestrom et al. (*J. Virology* 63: 4107-4113 (1991)).

The genotypes of the recombinant D2/IC-Px (where x = 5, 1, and/or 3 to indicate the incorporation of the parental [P in the virus designation] 16681 virus-specific 5'NC-57, NS1-53, and/or NS3-250 loci into the pD2/IC-VV45R [PDK-53] backbone) and D2/IC-Vx (where x indicates the reciprocal incorporation of the three candidate PDK-53 vaccine [V in the virus designation] virus-specific loci within the pD2/IC-30P-A [16681] backbone) viruses are shown in Table 11. If the 5'NC, NS1, and NS3 loci are the primary determinants of the PDK-53 virus-specific phenotype, then the D2/IC-P5 and D2/IC-V13 viruses should be equivalent (cognate) because both viruses contain 5'NC-57-C, NS1-53-Asp, and NS3-250-Val. The cognate virus pairs derived from reciprocal mutagenesis of the 16681 and PDK-53 virus-specific infectious clones are indicated in Table 11. To further investigate the prM-29 locus, we moved the prM-29-Asp locus of DEN-2 16681 virus into pD2/IC-VV45R and pD2/IC-P5 to derive recombinant D2/IC-Pp and -P5p viruses, respectively. Reciprocal recombinations yielded D2/IC-Vp and -V5p viruses.

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Each clone-derived virus (transfected BHK-21 seed) was propagated once in LLC-MK₂ cells. The genotypes of all of the LLC-MK₂-1-passaged, recombinant 16681/PDK-53 viruses were confirmed by complete nucleotide sequence analyses of their genomes. Because all of the viruses had the expected nucleotide sequences, we inferred that their cDNA clones were also correct. All of the clone-derived viruses contained the 16681 virus-specific nt-8571-C locus, which is the site of a silent mutation in PDK-53 virus. Direct sequencing of overlapping cDNA amplicons generated from DEN-2 viral genomic RNA using reverse transcriptase-polymerase chain reaction (RT-PCR) was used to determine the sequence of all but the termini of the cDNA. The sequences of the 5'- and 3'-terminal 30 nucleotides of the genome were determined by direct sequencing of the infectious clone cDNA in plasmid pBRUC-139. The D2/IC- prefix is eliminated in the virus designations in Table 11 and the following text.

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Characterization of the replication phenotypes of recombinant 16681/PDK-53 viruses.

Viruses were analyzed for plaque size, temperature sensitivity, and replication in LLC-MK₂ and C6/36 cells. Plaque sizes were evaluated after 9 days of incubation under agarose in LLC-MK₂ cell monolayers grown in 6-well plates. Viral growth curves were performed in 75-cm² flasks of LLC-MK₂ or C6/36 cells inoculated at multiplicity of infection (m.o.i.) of approximately 0.001 PFU/cell. After adsorption at 37°C for 2 h, 30 ml of DMEM medium (LLC-MK₂ cells) or overlay nutrient medium (C6/36 cells) containing penicillin/streptomycin and 5% FBS was added, and the cultures were incubated in 5% CO₂ at 37°C or 29°C, respectively. Aliquots of culture medium were removed at 48-h intervals, adjusted to 12.5% FBS, and stored at -80°C prior to virus titration.

Temperature sensitivity assays were performed in LLC-MK₂ cells grown in 75-cm² flasks. The cells were inoculated at a m.o.i. of about 0.001 PFU/cell. After adsorption for 2 h at 37°C, 30 ml of DMEM medium containing 5% FBS was added. One set of cultures was incubated for 8 days at 37°C, the other at 38.7°C. The ratio of virus titer at 38.7°C versus the titer at 37°C was calculated.

Mouse neurovirulence assay

Litters of newborn, outbred white ICR mice were inoculated intracranially with 10⁴ PFU of virus in a volume of 30 µl. Mice were individually weighed once a week and were observed for paralysis or death for 35 days.

Plaque phenotypes of recombinant 16681/PDK-53 viruses

Mean diameters of virus plaques (n=12) at 9 days after infection under agarose overlay in LLC-MK₂ cells were measured (FIG. 4). The largest plaques (3.2-3.4 mean diameter) were produced by the wild-type 16681 virus, its clone-derived 30P-A virus,

and the recombinant P513 virus, which contained the 5'NC, NS1, and NS3 16681 virus-specific loci in the VV45R (PDK-53) virus genetic background (Table 11). These three 16681-specific loci within the PDK-53 genetic background were sufficient to reconstitute the large plaque phenotype of the 16681 virus.

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Individual PDK-53 virus-specific 5'-NC-57-T, NS1-53-Asp, and NS3-250-Val mutations incorporated into the 16681 genotype each resulted in significantly ($p < 0.00003$) decreased plaque sizes of 2.1-2.3 mm in V5, V1, and V3 viruses, respectively, versus those of 16681 virus. The plaque phenotypes of P13 and P51 viruses were similar to those of their cognate V5 and V3 viruses (indicated by graph bars with identical solid or cross-hatching pattern in FIG. 4). The 2.8-mm plaque size of P53 virus differed from 16681 viral plaques to a lesser degree ($p < 0.03$) than did the 2.1-mm plaques of its cognate V1 virus. The 1.1 - 1.6-mm plaques of cognate virus pairs V13 (P5) (containing PDK-53 virus-specific NS1 and NS3 loci), V53 (P1) (PDK-53 virus-specific 5'NC and NS3 loci), and V51 (P3) virus (PDK-53 virus-specific 5'NC and NS1 loci) were essentially equivalent to the 1.3-mm plaques of PDK-53 virus. These results indicate that all pairwise combinations of these three PDK-53 virus-specific loci in the 16681 backbone generated a small-plaque virus similar to PDK-53 virus. Although V51 virus produced a plaque phenotype that was similar to that of PDK-53 virus, all three 16681 virus-specific 5'NC-C, NS1-53-Gly, and NS3-250-Glu loci were required within the PDK-53 background of P513 virus to reconstitute the plaque phenotype of 16681 virus. The presence of all three PDK-53 loci in the 16681 backbone generated V513 virus, which had a smaller ($p < 0.001$, Student's *t* test) plaque phenotype than that of either PDK-53 or VV45R virus. The difference between the plaque size of PDK-53 virus and that of VV45R virus was not significant.

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Recombinant Vp virus, which contained the PDK-53 virus-specific prM-29-Val locus in the 16681 background, had a significantly ($p < 0.002$) reduced plaque size of 2.6 mm. However, the 1.0-mm plaque phenotype of Pp virus (16681 prM-29-Asp locus in the PDK-53 background) was essentially identical to the 1.1-mm and 1.3-mm

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plaques of VV45R and PDK-53 viruses (FIG. 4A), respectively. The prM-29 locus did not affect the plaque phenotypes of P5p (1.0 ± 0.0 mm) and V5p (2.0 ± 0.4 mm) viruses, which produced plaques similar to those of P5 (1.1 ± 0.3 mm) and V5 (2.3 ± 0.4 mm), respectively.

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Replication of recombinant 16681/PDK-53 viruses in LLC-MK₂ and C6/36 cells

All of the viruses replicated well in LLC-MK₂ cells, reaching peak titers of $10^{7.3}$ - $10^{7.9}$ PFU/ml at 6-8 days after infection. PDK-53 and its clone-derived VV45R virus replicated at a reduced rate during the first four days after infection, relative to the other viruses. To determine temperature sensitivities, virus-infected LLC-MK₂ cells were incubated at 37°C or 38.7°C in 2-5 experiments (FIG. 4B). Temperature sensitivity scores were determined at 8 days after infection. All of the viruses exhibited some degree of temperature sensitivity under these conditions. In individual experiments, wild-type 16681 virus showed 75-80% titer reduction at 38.7°C. Virus V1 and cognate viruses P3 (V51), which showed 84-86% average reductions in titer, were slightly more temperature-sensitive than 16681 virus. However, only PDK-53, VV45R, V513, P5p, Pp, and the cognate recombinant viruses V13 and P5, all of which contained both the NS1-53-Asp and NS3-250-Val PDK-53 virus- specific loci, reproducibly showed 90-97% average reduction in titer at 38.7°C.

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The 16681 virus and its clone-derived 30P-A virus replicated to average peak titers of $10^{8.6}$ - $10^{8.8}$ PFU/ml at 12 days after infection in two independent growth-curve experiments in C6/36 cells (FIG. 4C). The replication of PDK-53 virus (peak titer of $10^{4.5}$ PFU/ml) and its clone- derived VV45R (peak titer of $10^{4.6}$ PFU/ml) virus was approximately 15,000-fold less efficient in C6/36 cells. The 16681 virus-specific 5'NC and NS1 loci within the PDK-53 background of P51 virus fully reconstituted the replication efficacy to that of wild-type 16681 virus. Conversely, the PDK-53 virus-specific 5'NC and NS1 loci within the 16681 background of V51 virus were sufficient to establish the crippled replication phenotype of PDK-53 virus. Recombinant cognate virus pairs V5 (P13) and V1 (P53), which contained the PDK-53 virus- specific 5'NC

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region or NS1 locus, respectively, replicated to average peak titers of $10^{5.9} - 10^{6.7}$ PFU/ml. Although the average peak titer of V53 virus was about 40-fold greater than that of V5 virus in C6/36 cells, the peak titers of P513, P13, P53, V3, V13, V513, and P3 viruses were very similar to those of P51, P1, P5, 30P-A, V1, V51, and VV45R viruses, respectively. These data indicated that the NS3-250 locus had little or no observable effect on replication in C6/36 cells (FIG. 4C). Vp and 16681 viruses had nearly equal average peak titers in C6/36 cells, as did P5 and P5p viruses. Pp and V5p viruses produced average peak titers that were slightly higher (8- and 40-fold, respectively) than those of PDK-53 and V5 viruses, respectively. The prM-29 locus appeared to have little or no effect on viral replication in C6/36 cells.

Neurovirulence of recombinant 16681/PDK-53 viruses in newborn mice

To investigate the neurovirulence of the recombinant viruses, two litters of newborn white ICR mice, eight mice per litter, were infected intracranially with 10^4 PFU of virus. The DEN-2 16681 virus and its clone-derived 30P-A virus cause 50%-100% mortality in these mice. Average survival times (AST) for mice succumbing to challenge with 16681 or 30P-A virus ranged from 15.2 to 16.8 days in various experiments. Mice were weighed individually every 7 days after infection. A single mouse died by day 1 after infection, presumably as a result of inoculation trauma, in each of the P53 and Vp groups (Table 12). These two mice were excluded from the analyses. There were no fatalities and no weight loss in the control, diluent-inoculated group.

Three mouse neurovirulence phenotypes were observed (Table 12). The first phenotype consisted of the mouse-virulent viruses DEN-2 16681, 30P-A, P513, P51, V3, and Vp, which caused at least 50% mortality with AST of 13.2-17.0 days (Table 12). In two other independent experiments, the Vp virus caused 46.67% mortality with AST of 17.4 ± 1.4 days ($n=16$) and 56.25% mortality with AST of 18.3 ± 1.3 days ($n=16$). In an independent experiment, P51 virus caused only 25% mortality with AST of 15.9 ± 5.5 days ($n=16$). A second phenotype consisted of the mouse-attenuated

PDK-53, VV45R, V513, Pp, and cognate V51 (P3) viruses, which caused no mortality, and the nearly attenuated V1, cognate V13 (P5), P5p, and V5p viruses, which killed only 1 of 16 mice (Table 12). The presence of the two PDK-53 virus-specific 5'NC-57-T and NS1-53-Asp loci within the 16681 genetic background was sufficient to result in or maintain attenuation in cognate viruses V51 (P3). Except for P53 virus, all of the viruses containing the PDK-53 virus-specific NS1-53-Asp locus were attenuated or nearly attenuated.

The third phenotype, that of intermediate virulence, characterized cognate virus pairs V5 (P13) and V53 (P1), and P53 virus which caused 18.75%-37.5% mouse mortality and significant weight loss ($p < 0.001$, Student's *t* test, at 3 weeks after infection, relative to diluent-inoculated control mice) in mice that survived virus challenge. Viruses V5 (P13) and V53 (P1) contained the 5'NC-57-T, but not the NS1-53-Asp, locus of PDK-53 virus. V1 virus (6.25% mortality) was more attenuated than V5 virus, which produced 18.75% mortality and significant weight loss in the survivors. Conversely, the 16681 virus-specific 5'-NC-57-C locus caused little reversion to virulence in P5 virus (6.25% mortality), whereas the NS1-53-Gly moiety in P1 virus resulted in an intermediate level (37.5%) of mortality and significant weight loss in the survivors. Unlike the nearly attenuated cognate V1 virus, P53 virus had an intermediate virulence phenotype. The NS1-53 locus had a more significant effect on the virulence phenotype than did the 5'-NC-57 locus.

The prM-29 locus showed no effect in P5p, Pp, and Vp viruses, relative to P5, PDK-53, and 16681 viruses, respectively. The V5p virus, which contained both PDK-53 virus-specific 5'NC-57-T and prM-29-Val loci, was nearly attenuated (Table 2). The NS3-250 locus did not appear to contribute significantly to mouse neurovirulence phenotype in V3, P13, V53, V13, and P3 viruses, which exhibited phenotypes that were

equivalent to 16681, P1, V5, V1, and PDK-53 viruses, respectively. The difference in the level of mortality caused by P53 and P5 viruses suggested that the 16681 virus-specific NS3-250-Glu locus might contribute somewhat to the virulence phenotype within certain genetic contexts.

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Evolution of mutations in the DEN-2 PDK-53 vaccine virus

Intermediate passages PDK-5, -10, -14, -35, and -45 of the 16681 virus were analyzed to determine the accrual of the nine nucleotide mutations in the PDK-53 vaccine strain. Amplicons were amplified directly from genomic mRNA extracted from the viral seed by RT/PCR. Automated sequencing of small genomic regions, which contained the nine relevant loci, was performed by using appropriate primers. The nucleotide residues identified at each of the nine loci for these viruses are shown in Table 13. The NS2A-181 Leu-to-Phe mutation and the silent mutations at E-37, NS3-342, and NS5-334 appeared by passage PDK-5 and were the predominant moieties by passage PDK-10 (NS2A-181), PDK-14 (E-373, NS3-342), or PDK-35 (NS5-334). Mutations 5'-NC-57 C-to-T, prM-29 Asp-to-Val, NS1-53 Gly-to-Asp, and NS4A-75 Gly-to-Ala occurred by passage PDK-35. The 5'-NC-57-T was predominant at passage PDK-35, while the other listed mutations became predominant by passage PDK-45. The NS3-250 Glu-to-Val mutation appeared by passage PDK-45 and is not fully mutated to the virus-specific Val in the current PDK-53 vaccine candidate (Table 13). Approximately 29% of the viral population in the PDK-53 vaccine contains NS3-250-Glu. The PDK-45 virus was genetically equivalent to the PDK-53 vaccine virus. In the present study, no attempt was made to determine the relative proportions of the two nucleotides at the mixed genetic loci shown in Table 13.

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Example 6

Construction of chimeric DEN-2/West Nile clones and virus

Genome-length, chimeric DEN-2/WN infectious cDNA clones containing structural genes of WN virus within the genetic background of DEN-2 virus were

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constructed using the *in vitro* ligation strategy used to derive the chimeric DEN-2/3 viruses described earlier.

- In a first example, the prM-E encoding cDNA of the 5'-end subclone that was used to derive a chimeric DEN-2/3-PP1 virus clone (see Example 2) was replaced with the prM-E gene region of WN virus, strain NY 99 (New York 1999). The cDNA fragment containing the prM-E gene region of WN virus was amplified by reverse transcriptase-polymerase chain reaction (RT-PCR) from WN virus-specific genomic RNA with forward primer WN-M
- (5'-GGAGCAGTTACCCTCTCTACGCGTCAAGGGAAGGTGATG-3' (SEQ ID NO:37); underlined MluI site followed by WN virus sequence near the 5' end of the prM gene) and reverse primer cWN-E
- (5'-GAAGAGCAGAACTCCGCCGCTGCGAGAAACGTGA GAGCTATGG-3' (SEQ ID NO:38); underlined NgoMIV site followed by sequence that was complementary to the WN genomic sequence near the 3' end of the E gene of WN virus). The amplified prM-E cDNA fragment was cloned into the MluI-NgoMIV sites of the intermediate pD2I/D3-P1-AscI clones, exactly as was done during the derivation of chimeric DEN-2/3 virus (see Example 2, construction of chimeric DEN-2/3 infectious clones), to replace the prM/E region of the DEN-3 16562 virus. In this chimeric DEN-2/WN cDNA, the prM splice site encoded the amino acid sequence (shown as single-letter amino acid abbreviations, and written in amino-to-carboxyl order) SAGMIIMLIPTVMA-FHLTTR*QGKVMMTV* (SEQ ID NO:39). The hyphen in this sequence indicates the polypeptide cleavage site located between the capsid and prM genes; the amino-terminal sequence is DEN-2 virus specific; the carboxyl-terminal sequence in bold, underlined, italicized font indicates the WN virus-specific sequence (*QGKVMMTV*) (SEQ ID NO:40) near the amino terminus of the prM protein encoded by this chimeric construct. This intermediate DEN-2/WN subclone was ligated *in vitro* with the 3'-end intermediate DEN-2 subclone, pD2-Pm⁺b-Asc, by the same protocol described in example 2 (construction of chimeric DEN-2/3 infectious clones) to produce the full genome-length, chimeric DEN-2/WN viral cDNA that was used to

transcribe chimeric DEN-2/WN virus-specific genomic RNA. Using the same protocol described in example 2, mammalian LLC-MK₂ or mosquito C6/36 cells were transfected with the transcribed chimeric DEN-2/WN RNA. This strategy, which involved using the same MluI restriction enzyme splice site that was used to derive the

5 chimeric DEN-2/3 and DEN-2/4 viruses, failed to produce viable chimeric virus after transfection of the transcribed chimeric DEN-2/WN RNA in LLC-MK₂ cells, and resulted in only very low titers (< 100 PFU/ml) in C6/36 cells. This failure is probably due to significant gene sequence variation between the carboxyl-terminal ends of the viral capsid proteins and between the amino-terminal ends of the prM protein of DEN-2

10 and WN viruses. The carboxyl-terminal region of the flavivirus capsid protein serves as a signal peptide sequence for the insertion of prM into intracellular membranes (endoplasmic reticulum) during maturation and cleavage of the prM protein. This DEN-2/WN construct, which contained the capsid-carboxyl-terminal signal sequence, as well as the amino-terminal residues of the prM protein of the DEN-2 backbone,

15 apparently did not permit appropriate maturation of the chimeric virus.

In a second example, the chimeric DEN-2/WN cDNA clone was modified so as to encode the carboxyl-terminal region of the capsid protein, as well as the entire prM protein and most of the E protein, of WN virus. A unique SstII restriction site was

20 introduced by site-directed mutagenesis near the 3' terminus of the DEN-2 virus-specific capsid gene to serve as a new 5' splice site for the WN capsid-carboxyl-end/prM/E gene region. This SstII site introduced two silent mutations in the DEN-2 virus-specific sequence encoding the amino acid triad SAG (single-letter abbreviations). The appropriate gene region was amplified from WN viral RNA by

25 using the forward primer WN-452.SAG
(5'-AATTCAACGCGTACATCCGCGGGCACCGGAATTGCAGTCA
TGATTGGCCTGATGGC-3' (SEQ ID NO:41); underlined SstII site followed by WN virus-specific sequence) and the same reverse cWN-E primer that was utilized in the previous construct (as described above). This amplified cDNA was cloned to make the

30 intermediate subclone pDEN-2/WN-P-SA which contained cDNA encoding the 5'

- noncoding region and most of the capsid gene from DEN-2 16681 virus and the carboxyl-terminal capsid, entire prM, and most of the E gene from WN virus, as well as a unique AscI site downstream of the NgoMIV site. In this chimeric DEN-2/WN cDNA, the prM splice site encoded the amino acid sequence (shown as single-letter amino acid abbreviations, and written in amino-to-carboxyl order)
- 5 SAGTGLIAMIGLIASVGA-VTLN**SNFOGKVMMTV** (SEQ ID NO:42). The hyphen in this sequence indicates the polypeptide cleavage site located between the capsid and prM genes; the amino-terminal sequence is DEN-2 virus specific; the carboxyl-terminal sequence in bold, underlined, italicized font indicates the WN virus-specific sequence
- 10 (TGIAVMIGLIASVGA-VTLN**SNFQGKVMMTV**) (SEQ ID NO:43) encoded by this chimeric construct. Following the *in vitro* ligation protocol of the chimeric DEN-2/3 clones described for chimeric DEN-2/3 virus in example 2, the 5'-end intermediate subclone pDEN-2/WN-P-SA was ligated to the 3'-end pD2-Pm^b-Asc subclone to produce the full genome-length cDNA of the chimeric DEN-2/WN-PP1 virus for
- 15 transcription of the chimeric RNA. The chimeric DEN-2/WN-PP1 construct encoded the indicated WN structural gene region within the genetic background of the wild-type DEN-2 16681 virus. Both LLC-MK₂ and C6/36 cells were transfected with RNA transcribed from this *in vitro*-ligated, chimeric DEN-2/WN-PP1 clone. Viable, chimeric DEN-2/WN-PP1 virus, at virus titers of 10³-10⁶ PFU/ml of culture medium,
- 20 was successfully recovered from both transfected cell cultures. Nucleotide sequence analysis of the entire genome of the clone-derived, chimeric DEN-2/WN virus demonstrated the expected genomic sequence. These results demonstrate that the DEN-2 infectious clones of the invention can be used to construct chimeric viruses that express structural genes of heterologous flaviviruses other than DEN-1, DEN-3, and
- 25 DEN-4 viruses.

All of the patents, publications and other references mentioned herein are hereby incorporated in their entirety by reference. Modifications and variations of the

present methods and compositions will be obvious to those skilled in the art from the foregoing detailed description. Such modifications and variations are intended to come within the scope of the appended claims.

Table 1

Viral Candidates for Flavivirus Chimeras⁺Primary Mosquito-Borne Species

Dengue-1 **
 Dengue-3 **
 Dengue-4 **
 Yellow fever **
 Japanese encephalitis **
 Murray Valley encephalitis **
 St. Louis encephalitis **
 West Nile **
 Kunjin *

Other Mosquito-Borne:Species

Alfuy
 Bagaza
 Banzi **
 Bouboui
 Bussuquara **
 Edge Hill **
 Ilheus
 Naranjal
 Israel turkey meningitis
 Jagra
 Kokobera
 Ntaya
 Rocio **
 Sepik **
 Spondweni **
 Stratford
 Tembusu
 Uganda S
 Usutu **
 Wesselsbron**
 Zika **

Tick-Borne:

Absettarov **
 Gadgets Gully
 Hanzalova **
 Hypr **
 Kadam
 Karshi
 Kumlinge **
 Kyasanur Forest disease **
 Langat
 Louping ill **
 Meaban
 Omsk hemorrhagic fever **
 Powassan **
 Royal Farm
 Russian spring
 summer encephalitis **
 Saumarez Reef
 Tyuleni

No Arthropod Vector Demonstrated

Apoi *
 Aroa
 Cacipacore
 Carey Island
 Cowbone Ridge
 Dakarbat **
 Entebbe bat
 Jutiapa
 Koutango *
 Modoc *
 Montana Myotis leukemia
 Negishi **
 Phnom-Penh bat
 Rio Bravo **
 Saboya
 Sal Vieja
 San Perlita
 Sokuluk

* = Laboratory infection reported

** = Natural and laboratory infection reported

⁺ = List includes the currently classified members of the *Flavivirus* genus in the International Catalogue of Arboviruses, Including Certain Other Viruses of Vertebrates, Nick Karabatsos, ed. The American Society of Tropical Medicine and Hygiene. 1985.

Table 2
Summary Of Nucleotide And Amino Acid Differences Between The Genomes Of
DEN-1 16007 Virus And Its Vaccine Derivative,
Strain PDK-13

Genome	<u>Nucleotide</u>		<u>Amino Acid</u>		<u>Protein</u>	<u>Polypeptide</u>
<u>Position</u>	<u>16007</u>	<u>PDK-13</u>	<u>16007</u>	<u>PDK-13</u>	<u>Position</u>	<u>Position</u>
1323	T	C	Val	Ala	E-130	410
1541)	G	A	Glu	Lys	E-203	483
1543)	A	G				
1545	G	A	Arg	Lys	E-204	484
1567	A	G	Gln	Gln	E-211	491
1608	C	T	Ser	Leu	E-225	505
2363	A	G	Met	Val	E-477	757
2695	T	C	Asp	Asp	NS1-92	867
2782	C	T	Ala	Ala	NS1-121	896
5063	G	A	Glu	Lys	NS3-182	1657
6048	A	T	Tyr	Phe	NS3-510	1985
6806	A	G	Met	Val	NS4A-144	2238
7330	A	G	Gln	Gln	NS4B-168	2412
9445	C	T	Ser	Ser	NS5-624	3117

Table 3
Summary Of Nucleotide And Amino Acid Sequence Differences Between The
Genomes Of DEN-2 16681 Virus And Its
Vaccine Derivative, Strain PDK-53

Genome	<u>Nucleotide</u>		<u>Amino Acid</u>		<u>Protein</u>	<u>Polypeptide</u>
<u>Position</u>	<u>16681</u>	<u>PDK-53</u>	<u>16681</u>	<u>PDK-53</u>	<u>Position</u>	<u>Position</u>
57	C	T ^a	-	-		
524	A	T	Asp	Val	prM-29	
2055	C	T	Phe	Phe	E-373	653
2579	G	A	Gly	Asp	NS1-53	828
4018	C	T	Leu	Phe	NS2A-181	1308
5270	A	T/A	Glu	Glu/Val ^b	NS3-250	1725
5547	T	C	Arg	Arg	NS3-342	1817
6599	G	C	Gly	Ala	NS4A-75	2168
8571	C	T	Val	Val	NS5-334	2825

^[a] 5' noncoding region.

^[b] The PDK-53 vaccine contains two genetic variants at nt-5270.

Table 4
Summary Of Nucleotide And Amino Acid Differences Between The Genomes Of
DEN-3 16562 Virus And Its Vaccine Derivative,
Strain PGMK-30/Frhl-3

<u>Genome</u>	<u>Nucleotide</u>	<u>Amino Acid</u>			<u>Protein</u>	<u>Polypeptide</u>
<u>Nucleotide</u>		<u>PGMK-30</u>	<u>PGMK-30/</u>			
<u>Position</u>	<u>16562</u>	<u>FRhL-3</u>	<u>16562</u>	<u>FRhL-3</u>	<u>Position</u>	<u>Position</u>
550	C	T	Ala	Ala	prM-38	152
1521	C/T	C	Ser/Leu ^a	Ser	E-196	476
1813	G	A	Lys	Lys	E-293	573
1838	A	G	Ser	Gly	E-302	582
1913	G	A	Glu	Lys	E-327	617
2140	C	T	Ala	Ala	E-402	682
3725	T	C	Phe	Leu	NS2A-86	1211
4781	C	A	Gln	Lys	NS3-90	1563

^a Two significant genetic variants were located at nt-1521.

Table 5
Summary Of Nucleotide And Amino Acid Differences Between The
Genomes Of DEN-4 1036 Virus And Its Vaccine Derivative,
Strain PDK-48

<u>Genome</u>						
<u>Nucleotide</u>		<u>Nucleotide</u>		<u>Amino Acid</u>		<u>Protein</u>
<u>Position</u>	<u>1036</u>	<u>PDK-48</u>	<u>1036</u>	<u>PDK-48</u>	<u>Position</u>	<u>Polypeptide</u>
1211	T	C	Ile	Ile	E-91	370
1971	G	A	Glu	Lys	E-345	624
3182	G	C	Gln	His	NS1-253	1027
6660	C	T	Leu	Phe	NS4A-95	2187
6957	A	A/T	Ile	Ile/Phe	NS4B-44	2286
7162	T	C	Leu	Ser	NS4B-112	2354
7546	C	C/T	Ala	Ala/Val	NS4B-240	2366
7623	G	T/G	Asp	Tyr/Asp	NS5-21	2508

Table 6
**Summary Of Non-Silent Mutations Between The Genomes Of The Parent-
 Vaccine Strains Of DEN-1, DEN-2, DEN-3, And DEN-4 Viruses**

<u>Genome</u> <u>Nucleotide</u> <u>Position</u>	<u>DEN-1</u>	<u>DEN-2</u>	<u>DEN-3</u>	<u>DEN-4</u>
57		5'NC-57 c-t		
524		prM-29 D-V		
1323	E-130 V-A			
1521			E-196 S/L-S	
1541)	E-203 E-K			
1543)				
1545	E-204 R-K			
1608	E-225 S-L			
1838			E-302 S-G	
1913			E-327 E-K	
1971				E-345 E-K
2363	E-477 M-V			
2579		NS1-53 G-D		
3182				NS1-253 Q-H
3725			NS2A-86 F-L	
4018		NS2A-181 L-F		
4781			NS3-90 Q-K	
5063	NS3-182 E-K			
5270		NS3-250 E-V/E		
6048	NS3-510 Y-F			
6599		NS4A-75 G-A		
6660				NS4A-95 L-F
6806	NS4A-144 M-V			
6957				NS4B-44 I-I/F
7162				NS4B-112 L-S
7546				NS4B-240 A-A/V
7623				NS5-21 D-D/Y

Table 7
Immunogenicity of viruses in mice.
Plaque reduction-neutralization titer^a against DEN-1 16007 virus

	Experiment 1 ^b Primary	Boost	Experiment 2 ^b Primary	Boost
	Immunizing Pooled sera virus (Range)	Pooled sera (Range)	Pooled sera (Range)	Pooled sera (Range)
DEN-1 16007	80 (20 - 80)	2560 (80 - 20480)	80 (20 - 160)	2560 (160 - 5120)
D2/1-PP	80 ^c	5120 ^c	40 (10 - 160)	5120 (160 - 10240)
D2/1-EP	80 (20 - 320)	10240 (640 - 20480)	160 (20 - 320)	5120 (2560 - ≥ 10240)
D2/1-VP	40 (10 - 160)	2560 (160 - 5120)	80 (10 - 320)	5120 (40 - ≥ 10240)
DEN-1 PDK-13	10 (10 - 40)	80 ^c	40 (20 - 80)	320 (20 - 640)
D2/1-PV	10 (<10 ^d - 20)	80 ^c	40 (10 - 80)	2560 (20 - ≥ 10240)
D2/1-EV	20 (<10 ^d - 20)	80 ^c	40 (<10 ^d - 40)	160 (10 - 320)
D2/1-VV	10 (10 - 40)	80 ^c	40 (10 - 160)	160 (20 - 640)

^a Titers are the reciprocal dilution yielding at least 50% plaque reduction.

^b 3-week-old outbred ICR mice were immunized intraperitoneally with 10⁴ PFU of virus, and were boosted with the same virus dose 3 weeks later in experiment 1, or 6 weeks later in experiment 2. Primary = serum taken 20 days (experiment 1) or 41 days (experiment 2) after primary immunization. Boost = serum taken 21 days after boost in both experiments.

^c Individual titers were not determined.

^d Only one mouse serum titer was less than 10 in these groups.

^e Bold titers indicate the pooled sera titers were 4 fold higher than the titers calculated with 70% plaque reduction. All other pooled titers were either no different from or two fold higher than 70% plaque reduction titers.

Table 8
Neutralization of chimeric DEN viruses by standard antibodies

<u>Virus</u>	<u>Antibody</u>					
	<u>D1-AF^a</u>	<u>D2-AF^a</u>	<u>D2-H5^b</u>	<u>D3-AF^a</u>	<u>D3-8A1^b</u>	<u>D4-AF^a</u>
DEN-1 16007 ^c	1280 ^d	40	20	40	< 20	20
DEN-2/1-EP ^e	2560	;	;	;	;	;
DEN-2 16681 ^c	80	2560>	40960	40	< 20	40
DEN-3 16562 ^c	80	160	40	1280	5120	40
DEN-2/3-EP1 ^e	;	;	;	2560	20480	;
DEN-4 1036 ^c	20	40	< 20	80	< 20	1280
DEN-2/4-EP1 ^e	;	;	;	;	;	2560

^a AF = DEN-1 (D1), DEN-2 (D2), DEN-3 (D3), and DEN-4 (D4) virus-specific mouse ascitic fluids (polyvalent antisera).

^b DEN-2 and DEN-3 virus-specific, envelope glycoprotein-specific (E-specific) monoclonal antibodies D2-H5 and D3-8A1, respectively.

^c Wild-type DEN virus.

^d Reciprocal serum dilution-plaque reduction neutralization titers (50% endpoint) are shown;

; = not tested

^e Chimeric DEN-2/1-EP, DEN-2/3-EP1, or DEN-2/4-EP1 virus expressing structural genes of DEN-1 16007, DEN-3 16562, or DEN-4 1036 virus, respectively.

Table 9

Neurovirulence of chimeric DEN-2/3 and DEN-2/4 viruses in newborn

white ICR mice		
Challenge Virus ^a	Percent Mortality ^b	AST (SD) (days) ^c
DEN-3 16562 ^d	100.0	14.1 (2.1)
DEN-3 P30/FRhL-3 ^e	15.0	16.2 (3.2)
DEN-2/3-PP1 ^f	32.5	19.0 (2.1)
DEN-2/3-EP1 ^f	0.0	-
DEN-2/3-VP1 ^f	0.0	-
DEN-4 1036 ^d	100.0	8.6 (0.6)
DEN-4 PDK-48 ^e	100.0	10.7 (1.5)
DEN-2/4-PP1 ^f	62.5	17.8 (2.8)
DEN-2/4-EP1 ^f	0.0	-
DEN-2/4-VP1 ^f	0.0	-
DEN-2 16681 ^d	87.5	15.2 (2.6)
DEN-2 PDK53-E48 ^e	0.0	-
DEN-2 PDK53-V48 ^e	0.0	-
Diluent	0.0	-

^a Newborn mice were challenged intracranially with 10⁴ PFU of virus.

^b {Number of fatalities / total number (n=16) of mice challenged} x 100.

^c Average survival time (AST) and standard deviation (SD); - = not applicable, because there were no fatalities in this group.

^d Wild-type DEN serotype virus

^e Mahidol candidate DEN vaccine virus: DEN-3 = PGMK-30/FRhL-3 (P30/FRhL-3); DEN-4 = PDK-48; DEN-2 = PDK-53-E variant (NS3-250-Glu locus) and PDK-53-V variant (NS3-250-Val locus). Both PDK-53-E and -V variant viruses were derived from infectious cDNA clones of the variants.

^f Chimeric DEN-2/3 or DEN-2/4 virus. The prM/E gene region of DEN-3 16562 virus or DEN-4 1036 virus was expressed in the genetic background of wild-type DEN-2 16681 virus (PP1 viruses), Mahidol candidate vaccine DEN-2 PDK-53-E variant (EP1 viruses), or Mahidol candidate vaccine DEN-2 PDK-53-V variant (VP1 viruses).

Table 10
Protective efficacy of chimeric DEN-2/1 viruses in AG-129 mice^a

Reciprocal neutralizing antibody titer against appropriate homologous DEN-3 or DEN-4 virus at 4 or 6 weeks after immunization

<u>Immunizing Virus</u>	<u>4 weeks</u>	<u>6 weeks</u>
DEN-3 16562 ^b	320 ^c	640
DEN-3 P30/FRhL-3 ^d	160	320
DEN-2/3-EP1 ^e	80	320
DEN-4 1036 ^b	160	1280
DEN-4 PDK-48 ^d	80	320
DEN-2/4-EP1 ^e	20	40

^a AG-129 mice are an inbred strain that lack receptors for interferon alpha/beta and interferon gamma. Mice, 3.5 - 4.5 weeks in age, were immunized intraperitoneally with 10⁵ PFU of virus.

^b Wild-type DEN virus.

^c Reciprocal dilution of pooled serum that neutralized 70% or greater of the input wild-type DEN-3 16562 virus that was used to test sera from mice immunized with DEN-3 or chimeric DEN-2/3-EP1 virus, or the input wild-type DEN-4 1036 virus that was used to test sera from mice immunized with DEN-4 or chimeric DEN-2/4-EP1 virus.

^d Mahidol candidate vaccine virus, DEN-3 PGMK-30/FRhL-3 (P30/FRhL-3), DEN-4 PD-48.

^e Chimeric DEN-2/3-EP1 or DEN-2/4-EP1 expressing the prM/E gene region of DEN-3 16562 or DEN-4 1036 virus, respectively.

Table 11

Genotypes of recombinant DEN-2 16681/PDK-53 viruses

Clone-derived		<u>Dengue-2 16681 determinants in PDK-53 background^a</u>				
<u>virus (cognate)^b</u>	<u>5'NC-57</u>	<u>prM-29</u>	<u>NS1-53</u>	<u>NS2A-181</u>	<u>NS3-250</u>	<u>NS4A-75</u>
DEN-2 PDK-53	t	V	D	F	V	A
VV45R (V513)
P5 (V13)	c
P1 (V53)	.	.	G	.	.	.
P3 (V51)	E	.
P51 (V3)	c	.	G	.	.	.
P53 (V1)	c	.	.	.	E	.
P13 (V5)	.	.	G	.	E	.
P513 (30P-A)	c	.	G	.	E	.

<u>Dengue-2 PDK-53 determinants in 16681 background^a</u>						
	<u>5'NC-57</u>	<u>prM-29</u>	<u>NS1-53</u>	<u>NS2A-181</u>	<u>NS3-250</u>	<u>NS4A-75</u>
DEN-2 16681	c	D	G	L	E	G
30P-A (P513)
V5 (P13)	t
V1 (P53)	.	.	D	.	.	.
V3 (P51)	V	.
V51 (P3)	t	.	D	.	.	.
V53 (P1)	t	.	.	.	V	.
V13 (P5)	.	.	D	.	V	.
V513 (VV45R)	t	.	D	.	V	.

^a The genome of the candidate dengue-2 PDK-53 vaccine virus differs from that of its 16681 parent at nine nucleotide loci, including three silent mutations (not shown), a mutation at genome nucleotide position 57 in the 5' noncoding region (5'NC-57; lower case letters), and five nucleotides encoding amino acid mutations (upper case, single-letter abbreviations) at viral polypeptide positions premembrane (prM)-29, nonstructural protein 1 (NS1)-53, NS2A-181, NS3-250, and NS4A-75 (32). Genetic loci from the parental 16681 virus were engineered into the cDNA background of the PDK-53 virus-specific infectious clone, pD2/IC-VV45R. Dots indicate sequence identity with PDK-53 virus (NS3-250-Val variant). The candidate PDK-53 vaccine also contains a genetic variant that has Glu at NS3-250 (32).

^b The genotypes of wild-type DEN-2 16681 virus, its attenuated vaccine derivative, DEN-2 PDK-53 virus, infectious clone-derived VV45R (genetically equivalent to the PDK-53 NS3-250-Val variant) and 30P-A (equivalent to wild-type 16681) viruses, and recombinant 16681/PDK-53 viruses are shown. The numerical designations for recombinant Px and Vx viruses (where x = 5'NC, NS1, and/or NS3 loci) indicate parental (P in virus designation) 16681 virus-specific loci engineered into the PDK-53 virus-specific infectious cDNA clone (top series) or reciprocal candidate PDK-53 vaccine (V in virus designation) virus-specific loci engineered into the 16681 clone (bottom series), respectively. P5 and V13 are cognate viruses, assuming that the PDK-53 virus-specific phenotype is determined predominantly by the 5'NC-57, NS1-53, and NS3-250 loci. Both P5 and V13 viruses contain the 5'NC-57-c, NS1-53-Asp, and NS3-250-Val loci within the genetic backgrounds of PDK-53 and 16681 viruses, respectively.

^c Genetic loci from PDK-53 virus were engineered into the cDNA background of the 16681 virus-specific infectious clone, pD2/IC-30P-A. Dots indicate sequence identity with 16681 virus.

Table 12
Neurovirulence of DEN-2 16681, PDK-53, and recombinant 16681/PDK-53 viruses
in newborn white ICR mice

Mouse challenge ^a		Virus genotype ^b						
Virus (cognate) ^c	Mortality	AST (SD)	5'-NC	prM	NS1	NS2A	NS3	NS4A
	(%)	(days)	57	29	53	181	250	75
DEN-2 16681	68.75	15.2 (1.2)	c	D	G	L	E	G
30P-A (P513)	81.25	14.6 (2.3)
P513 (16681)	100.0	13.2 (1.6)	.	V	.	F	.	A
P51 (V3)	50.0 ^d	15.9 (5.5)	.	V	.	F	V	A
P1 (V53)	37.5 ^d	19.0 (4.2)	t	V	.	F	V	A
P13 (V5)	37.5 ^d	13.5 (2.1)	t	V	.	F	.	A
P53 (V1)	20.0 ^d	17.0 (7.8)	.	V	D	F	.	A
P5p (V13)	6.25	15.0	.	.	D	F	V	A
P5 (V13)	6.25	27.0	.	V	D	F	V	A
Pp (PDK-53)	0	- ^e	t	.	D	F	V	A
P3 (V51)	0	-	t	V	D	F	.	A
V3 (P51)	75.0 ^d	16.4 (3.2)	V	.
Vp (16681)	87.5	17.0 (0.9)	.	V
V53 (P1)	18.75 ^d	21.3 (6.1)	t	.	.	.	V	.
V5 (P13)	18.75 ^d	21.7 (4.2)	t
V5p (P13)	6.25	20.0	t	V
V13 (P5)	6.25	17.0	.	.	D	.	V	.
V1 (P53)	6.25	22.0	.	.	D	.	.	.
V51 (P3)	0	-	t	.	D	.	.	.
V513 (PDK-53)	0	-	t	.	D	.	V	.
VV45R (V513)	0	-	t	V	D	F	V	A
DEN-2 PDK-53	0	-	t	V	D	F	V	A

^a Percent mortality and average survival time (AST) \pm standard deviation (SD) of newborn, outbred white ICR mice challenged intracranially with 10⁴ PFU of virus. Sixteen mice per group, except for the P53 and Vp groups in which a single mouse died by day 1 after infection, presumably as a result of inoculation trauma. These two mice were excluded from the study.

^b See text for explanation of virus genotypes. Solid dots indicate sequence identity with 16681 virus.

^c See text for explanation of virus and cognate virus designations.

^d Mean body weight of surviving mice was significantly lower ($p < 0.001$, Student's *t* test) than that of diluent-inoculated control mice (not shown) at 3 weeks after infection.

^e Average survival time is not applicable because there was no mortality in this mouse group.

Table 13
Evolution of DEN-2 virus, vaccine strain PDK-53, during passage of the parental
16681 strain in primary dog kidney (PDK) cells

Genome nucleotide position ^a / Translated polypeptide position ^b / Encoded amino acids ^c									
	57 ^a	524	2055	2579	4018	5270	5547	6599	8571
		prM-29 ^b	E-373	NS1-53	NS2A-181	NS3-250	NS3-342	NS4A-75	NS5-334
<u>Virus</u>		<u>D - V^c</u>	<u>F - F</u>	<u>G - D</u>	<u>L - F</u>	<u>E - V</u>	<u>R - R</u>	<u>G - A</u>	<u>V - V</u>
16681	C ^d	A	C	G	C	A	T	G	C
PDK-5	C	A	C/T ^e	G	T/C	A	T/C	G	C/T
PDK-10	C	A	T/C	G	T	A	C/T	G	T/C
PDK-14	C	A	T	G	T	A	C	G	T/C
PDK-35	T	T/A	T	A/G	T	A	C	C/G	T
PDK-45	T	T	T	A	T	A/T	C	C	T
PDK-53	T	T	T	A	T	A/T	C	C	T

^a Genome nucleotide positions of the nine nucleotide sequence differences between 16681 and PDK-53 viruses. Nucleotide position 57 lies within the 5' noncoding region of the viral genome.

^b Protein designations are as follows: prM = premembrane protein; E = envelope glycoprotein; NS = nonstructural protein.

^c The virus-specific amino acid residues (16681 - PDK-53) are shown for each amino acid position.

^d A, C, G, and T (cDNA sense) nucleotides are indicated.

^e Two genetic populations were identified for this locus in the virus. The order of the two nucleotides reflects relative peak heights of the nucleotide signals in sequence chromatograms.

Table 14**Conservation of DEN-2 PDK-53 phenotypic attenuation markers
in chimeric DEN viruses.**

<u>Attenuation phenotype</u>	<u>DEN virus</u>			
	<u>DEN-2*</u>	<u>DEN-2/1</u>	<u>DEN-2/3</u>	<u>DEN-2/4</u>
Attenuation in mice	+	+	+	+
Decreased replication in C6/36 cells	+	+	+	+
Small plaques in LLC-MK ₂ cells	+	+	+	+
Temperature sensitivity in LLC-MK ₂ cells	+	+	+	+

* Mahidol candidate DEN-2 PDK-53 vaccine virus. The chimeric DEN-2/1, DEN-2/3, and DEN-2/4 viruses were constructed in the DEN-2 PDK-53 genetic background, NS3-250-Val or -Glu variant. The phenotypes shown for chimeric viruses are representative of chimeric viruses constructed in the background of either variant of DEN-2 PDK-53 virus.

Table 15

**Diagnostic Genetic Probes and Amplimers for the Candidate Mahidol
DEN-1, DEN-2, DEN-3, and DEN-4 Vaccine Viruses.**

Genetic Locus: D1V-1323 = Mutated genetic locus for candidate DEN-1 PDK-13 vaccine (V) virus at genome nucleotide position 1323.

Primer designations: p = TaqMan probe sequence, mRNA-sense
 pc = TaqMan probe sequence, complementary-sense
 f = forward amplimer, mRNA-sense
 r = reverse amplimer, complementary-sense
 SEQ ID = probe or primer sequence.

<u>Genetic Locus</u>	<u>Primer Designation</u>	<u>SEQ ID NO:</u>
D1V-1323		
Probe	pcD1V-1308	44
F	fd1V-1298	45
R	rd1V-1347	46
D1V-1541, 1543, 1545		
Probe	pcD1V-1530	47
F	fd1V-1519	48
R	rd1V-1567	43
D1V-1567		
Probe	pD1V-1580	50
F	fd1V-1545	51
R	rd1V-1608	52
D1V-1608		
Probe	pcD1V-1595	53
F	fd1V-1567	54
R	rd1V-1626	55
D1V-2363		
Probe	pD1V-2374	56
F	fd1V-2334	57
R	rd1V-2386	58
D1V-2695		
Probe	pcD1V-2686	59
F	fd1V-2660	60
R	rd1V-2735	61
D1V-2782		
Probe	pD1V-2767	62
F	fd1V-2752	63
R	rd1V-2801	64

Table15 (continued)**Diagnostic Genetic Probes and Amplimers for the Candidate Mahidol
DEN-1, DEN-2, DEN-3, and DEN-4 Vaccine Viruses.**

<u>Genetic Locus</u>	<u>Primer Designation</u>	<u>SEQ ID NO:</u>
D1V-5063		
Probe	pcD1V-5052	65
F	fd1V-5040	66
R	rd1V-5095	67
D1V-6048		
Probe	pD1V-6059	68
F	fd1V-6030	69
R	rd1V-6069	70
D1V-6806		
Probe	pcD1V-6793	71
F	fd1V-6780	72
R	rd1V-6825	73
D1V-7330		
Probe	pD1V-7343	74
F	fd1V-7310	75
R	rd1V-7351	76
D1V-9445		
Probe	pcD1V-9433	77
F	fd1V-9419	78
R	rd1V-9485	79
D2V-57		
Probe	pD2V-69	80
F	fd2V-32	81
R	rd2V-81	82
D2V-524		
Probe	pcD2V-513	83
F	fd2V-492	84
R	rd2V-551	85
D2V-2055		
Probe	pD2V-2067	86
F	fd2V-2025	87
R	rd2V-2080	88
D2V-2579		
Probe	pcD2V-2568	89
F	fd2V-2535	90
R	rd2V-2603	91

Table15 (continued)**Diagnostic Genetic Probes and Amplimers for the Candidate Mahidol
DEN-1, DEN-2, DEN-3, and DEN-4 Vaccine Viruses.**

<u>Genetic Locus</u>	<u>Primer Designation</u>	<u>SEQ ID NO:</u>
D2V-4018		
Probe	pD2V-4030	92
F	fD2V-3993	93
R	rD2V-4043	94
D2V-5270-E		
D2V-5270-V		
ProbeE	pD2VE-5279	95
ProbeV	pD2VV-5279	96
F	fD2V-5243	97
R	rD2V-5295	98
D2V-5547		
Probe	pD2V-5558	99
F	fD2V-5521	100
R	rD2V-5589	101
D2V-6599		
Probe	pcD2V-6588	102
F	fD2V-6569	103
R	rD2V-6625	104
D2V-8571		
Probe	pD2V-8582	105
F	fD2V-8535	106
R	rD2V-8594	107
D3V-550		
Probe	pD3V-562	108
F	fD3V-525	109
R	rD3V-575	110
D3V-1521		
Probe	pD3V-1533	111
F	fD3V-1497	112
R	rD3V-1541	113
D3V-1813		
Probe	pcD3V-1804	114
F	fD3V-1767	115
R	rD3V-1838	116
D3V-1838		
Probe	pcD3V-1827	117
F	fD3V-1813	118
R	rD3V-1913	119

Table15 (continued)

**Diagnostic Genetic Probes and Amplimers for the Candidate Mahidol
DEN-1, DEN-2, DEN-3, and DEN-4 Vaccine Viruses.**

<u>Genetic Locus</u>	<u>Primer Designation</u>	<u>SEQ ID NO:</u>
D3V-1913		
Probe	pcD3V-1903	120
F	fd3V-1891	121
R	rd3V-1967	122
D3V-2140		
Probe	pcD3V-2127	123
F	fd3V-2116	124
R	rd3V-2188	125
D3V-3725		
Probe	pD3V-3738	126
F	fd3V-3698	127
R	rd3V-3745	128
D3V-4781		
Probe	pcD3V-4772	129
F	fd3V-4762	130
R	rd3V-4801	131
D4V-1211 (T-C)		
Probe	pD4V-1222	132
F	fd4V-1191	133
R	rd4V-1250	134
D4V-1971 (G-A)		
Probe	pcD4V-1957	135
F	fd4V-1943	136
R	rd4V-2010	137
D4V-3182 (G-C)		
Probe	pD4V-3193	138
F	fd4V-3154	139
R	rd4V-3227	140
D4V-6660 (C-T)		
Probe	pcD4V-6648	141
F	fd4V-6638	142
R	rd4V-6688	143
D4V-7162 (T-C)		
Probe	pD4V-7174	144
F	fd4V-7141	145
R	rd4V-7188	146

Table 16

SEQ ID NO: for TaqMan probes and amplimers.

Underlined residues indicate the positions of the candidate vaccine virus mutation within the primer sequence, or, in the case of SEQID #52, the underlined residue indicates the nt-5270 position of DEN-2 16681 virus.

SEQ ID NO:

```

44  5'-TTCATATTGAGCTATCTTTTCCTTCTA-3'
45  5'-GTGTGCCAAGTTTAAGTGTG-3'
46  5'-TGGACGGTGACTATCACTG-3'
47  5'-AAGCCATGATTTCTTTTCATTGTCA-3'
48  5'-CAGGGCTAGATTTTAACGAG-3'
49  5'-AGTGGTAAGTCTAGAAACCCAC-3'
50  5'-TCCACAAACAGTGGTTTCTAGACT-3'
51  5'-TGTGTGCTGACAATGAAAAAGAA-3'
52  5'-TCCAAGTCTCTTGGGATGTTA-3'
53  5'-TGGGATGTTAAAGCCCCAGAGGT-3'
54  5'-TCATGGCTTGTCCACAAACAG-3'
55  5'-CCAGTAAATCTTGTCTGTTCC-3'
56  5'-CGTCCCTTTTCGGTGATGTGCATC-3'
57  5'-ATTCTGCTGACATGGCTAGG-3'
58  5'-TCCTAGGTACAGTGTGACC-3'
59  5'-AGATTCCACTAACGTCTCCACG-3'
60  5'-AATTGAACCACATCCTACTTG-3'
61  5'-TTGTGTTCCATGGGTTGTGG-3'
62  5'-TATGATTTTAGCTTTTCCCAGCTT-3'
63  5'-GCCACAACCCATGGAACAC-3'
64  5'-ATGAAGGTGGTGTCTGTAC-3'
65  5'-TCCTAAACACCTTGTCTCAATCT-3'
66  5'-GCTAAGGCATCACAAGAAGG-3'
67  5'-CGATCCTGGATGTAGGTCC-3'
68  5'-CAGCCCTCTTTGAGCCGGAGA-3'
69  5'-AATAATAACACACCAGAAGG-3'
70  5'-TCCCCGTCTATAGCTGCAC-3'
71  5'-TGTCAAATATCAGGAATAACAGACCT-3'
72  5'-CACAGGACAACCCAGCTAGC-3'
73  5'-AATAATCCCATCTCATTGG-3'
74  5'-ATTTGAAAAACAGCTAGGCCAAATAA-3'
75  5'-CTTAGATCCCGTGGTTTACG-3'
76  5'-AATCTGTGATGTGCAAAGTATC-3'
77  5'-AAAGATTCCCTCAGACTCCATTTGT-3'
78  5'-CACTTTCACCAACATGGAGG-3'

```

Table 16 (continued)

SEQ ID NO: for TaqMan probes and amplimers.

79	5'-CGAGAACTCTTCCGGCTAG-3'
80	5'-AGCTAAGCTCAATGTAAGTCTAACA-3'
81	5'-CGTGGACCGACAAAGACAG-3'
82	5'-TCATCAGAGATCTGCTCTCT-3'
83	5'-ATGTTACGCCCACCTCTGTTTTA-3'
84	5'-GATCGTCAGCAGACAAGAG-3'
85	5'-CAATTCACCAAGGTCCATGG-3'
86	5'-AACCTCCATTGGGAGACAGCTAC-3'
87	5'-AATTGTGACAGAAAAAGATAGC-3'
88	5'-TCAGTTGTCCCGGCTCTAC-3'
89	5'-ATTCCACAAATGTCCTCTTCATGG-3'
90	5'-TACAAGTTCCAACCAGAATCC-3'
91	5'-CATCAGATTCTCCAGTCTTG-3'
92	5'-TTTCCCCTGTTCTTAACATCCT-3'
93	5'-GAAAGTGAGTTGCACAATATTG-3'
94	5'-ATGCTAATGGTATCCAATCTG-3'
95	5'-CATCAGAGCTGAGCACACCGG-3'
96	5'-CATCAGAGCTGTCACACCGG-3'
97	5'-CCTTAGAGGACTTCCAATAAG-3'
98	5'-AATGTGGCATGACACATTAGG-3'
99	5'-ATCCCTGAACGCTCGTGGAATTC-3'
100	5'-AGAGCAATGCACCAATCATAG-3'
101	5'-GAACGAACCAACAGTCTTC-3'
102	5'-TATGCCCCCTTGCCTCATCAAG-3'
103	5'-CACTTCTGGCTACAGTCAC-3'
104	5'-GTGATTATGCAGCACATTCC-3'
105	5'-CTTGGGACGTTGTCCCCATGGT-3'
106	5'-CAGCATCATCCATGGTCAAC-3'
107	5'-GGAGTCGTGTCTGTCAATTG-3'
108	5'-CACTCATAGCTATGGATCTGGGA-3'
109	5'-CTTTTCAAGACAGCCTCTGG-3'
110	5'-CATTGTAAAGTGACCGTGTG-3'
111	5'-CAATGAAATGATCTCATTGACAATGAA-3'
112	5'-AATGCTCACCACGACAGG-3'
113	5'-TTGTCTATGTACCATCCATGC-3'
114	5'-CATAGCTCATCCCTTTGAGTTCC-3'
115	5'-GAGGCACAAGTATCTTTGC-3'
116	5'-TTTCTTCAACACAAAGCTACC-3'
117	5'-ACACAAAGCTACCAAGCACATTG-3'
118	5'-GATGGACAAATTGGAACCTCAA-3'
119	5'-ATCTTGCAAGGTGCATCTTT-3'

Table 16 (continued)**SEQ ID NO: for TaqMan probes and amplimers.**

120	5'-AGGGTGCATCTT <u>T</u> CCCTTTGTAC-3'
121	5'-GCAGCATGGGACAATACTC-3'
122	5'-GTGATCAGTCTGCCATTGTG-3'
123	5'-CCTCTGGCAGT <u>A</u> GCCTCGAACATCT-3'
124	5'-ACTGGTACAAGAAGGGAAGC-3'
125	5'-ACCCACTGATCCAAAGTCC-3'
126	5'-TCAGCCA <u>C</u> TCCTGGCTTTGGG-3'
127	5'-GGCGTCACTTACCTAGCTC-3'
128	5'-TAGATGTCAGTTTCCTCAGG-3'
129	5'-CCTCCCCCTTTT <u>T</u> CCATTGTGC-3'
130	5'-TTTCATACGGAGGAGGATGG-3'
131	5'-AGGCTCTACGGCAATAACC-3'
132	5'-CAACAGTACAT <u>C</u> TGCCGGAGAGA-3'
133	5'-GAGAGCCTTATCTAAAAGAGG-3'
134	5'-CTTTTCCAAACAAGCCACAG
135	5'-AACCACTTTTT <u>T</u> CTTGTTACATCTC
136	5'-TGGAGCTCCGTGTAAAGTC-3'
137	5'-GCACTGTTGGTATTCTCAGC-3'
138	5'-CCCTTTTTCACAC <u>C</u> CACAATTACCG-3'
139	5'-GAAAGCCAGATGCTCATTCC-3'
140	5'-TATCTCTAATTGCCTAAGTGC-3'
141	5'-CTACCCAGA <u>A</u> CAAGCCACTAGC-3'
142	5'-ATTGTCAATGGGTTTGATAACC-3'
143	5'-TATGATTGAGGCCGCTATCC-3'
144	5'-TAGTCATGCTTT <u>C</u> AGTCCATTATGC-3'
145	5'-AGTGAACCCAACAACCTTTGAC-3'
146	5'-TGGCTTTTGCCTGCAATCC-3'

We claim:

1. A nucleic acid chimera comprising a first nucleotide sequence encoding nonstructural proteins from an attenuated dengue-2 virus and a second nucleotide sequence encoding a structural protein from a second flavivirus.
2. The nucleic acid chimera of claim 1, wherein the attenuated dengue-2 virus is vaccine strain PDK-53.
3. The nucleic acid chimera of claim 2, wherein the structural protein is selected from the group consisting of a C protein of dengue-1 virus, a prM protein of dengue-1 virus, an E protein of dengue-1 virus or any combination thereof.
4. The nucleic acid chimera of claim 2, wherein the structural protein is selected from the group consisting of a C protein of dengue-2 virus, a prM protein of dengue-2 virus, an E protein of dengue-2 virus or any combination thereof.
5. The nucleic acid chimera of claim 2, wherein the structural protein is selected from the group consisting of a C protein of dengue-3 virus, a prM protein of dengue-3 virus, an E protein of dengue-3 virus or any combination thereof.
6. The nucleic acid chimera of claim 5, wherein the structural protein is an E protein of dengue-3 virus and the E protein contains a leucine at amino acid position 345.
7. The nucleic acid chimera of claim 2, wherein the structural protein is selected from the group consisting of a C protein of dengue-4 virus, a prM protein of dengue-4 virus, an E protein of dengue-4 virus or any combination thereof.

8. The nucleic acid chimera of claim 7, wherein the structural protein is an E protein of dengue-4 virus and the E protein contains a leucine at amino acid position 447, and further comprises a C protein of dengue-2 virus and the C protein contains a serine at position 100.
9. The nucleic acid chimera of claim 8, further comprising a valine at position 364 of the E protein.
10. The nucleic acid chimera of claim 2, wherein the structural protein is selected from the group consisting of a C protein of West Nile virus, a prM protein of West Nile virus, an E protein of West Nile virus or any combination thereof.
11. The nucleic acid chimera of claim 2, wherein the structural protein is selected from the group consisting of a C protein of Japanese encephalitis virus, a prM protein of Japanese encephalitis virus, an E protein of Japanese encephalitis virus or any combination thereof.
12. The nucleic acid chimera of claim 2, wherein the structural protein is selected from the group consisting of a C protein of St. Louis encephalitis virus, a prM protein of St. Louis encephalitis virus, an E protein of St. Louis encephalitis virus or any combination thereof.
13. The nucleic acid chimera of claim 2, wherein the structural protein is selected from the group consisting of a C protein of tick-borne encephalitis virus, a prM protein of tick-borne encephalitis virus, an E protein of tick-borne encephalitis virus or any combination thereof.
14. The nucleic acid chimera of claim 2, wherein the structural protein is selected from the group consisting of a C protein of yellow fever virus, a prM protein of yellow fever virus, an E protein of yellow fever virus or any combination thereof.

15. The nucleic acid chimera of claim 2, wherein the second flavivirus is a virulent strain.
16. The nucleic acid chimera of claim 15, wherein the structural protein is selected from the group consisting of a C protein of dengue-1 virus, a prM protein of dengue-1 virus, an E protein of dengue-1 virus or any combination thereof.
17. The nucleic acid chimera of claim 15, wherein the structural protein is selected from the group consisting of a C protein of dengue-2 virus, a prM protein of dengue-2 virus, an E protein of dengue-2 virus or any combination thereof.
18. The nucleic acid chimera of claim 15, wherein the structural protein is selected from the group consisting of a C protein of dengue-3 virus, a prM protein of dengue-3 virus, an E protein of dengue-3 virus or any combination thereof.
19. The nucleic acid chimera of claim 18, wherein the structural protein is an E protein of dengue-3 virus and the E protein contains a leucine at position 345.
20. The nucleic acid chimera of claim 15, wherein the structural protein is selected from the group consisting of a C protein of dengue-4 virus, a prM protein of dengue-4 virus, an E protein of dengue-4 virus or any combination thereof.
21. The nucleic acid chimera of claim 20, wherein the structural protein is an E protein of dengue-4 virus and the E protein contains a leucine at amino acid position 447, and further comprises a C protein of dengue-2 virus and the C protein contains a serine at position 100.
22. The nucleic acid chimera of claim 21, further comprising a valine at position 364 of the E protein.

23. The nucleic acid chimera of claim 15, wherein the structural protein is selected from the group consisting of a C protein of West Nile virus, a prM protein of West Nile virus, an E protein of West Nile virus or any combination thereof.
24. The nucleic acid chimera of claim 15, wherein the structural protein is selected from the group consisting of a C protein of Japanese encephalitis virus, a prM protein of Japanese encephalitis virus, an E protein of Japanese encephalitis virus or any combination thereof.
25. The nucleic acid chimera of claim 15, wherein the structural protein is selected from the group consisting of a C protein of St. Louis encephalitis virus, a prM protein of St. Louis encephalitis virus, an E protein of St. Louis encephalitis virus or any combination thereof.
26. The nucleic acid chimera of claim 15, wherein the structural protein is selected from the group consisting of a C protein of tick-borne encephalitis virus, a prM protein of tick-borne encephalitis virus, an E protein of tick-borne encephalitis virus or any combination thereof.
27. The nucleic acid chimera of claim 15, wherein the structural protein is selected from the group consisting of a C protein of yellow fever virus, a prM protein of yellow fever virus, an E protein of yellow fever virus or any combination thereof.
28. A nucleic acid chimera comprising a first nucleotide sequence encoding nonstructural proteins from an attenuated dengue-2 virus, and at least two different nucleotide sequences, each encoding a structural protein from at least two different flaviviruses.
29. The nucleic acid of claim 28, wherein the attenuated dengue-2 virus is vaccine strain PDK-53.

30. The nucleic acid chimera of claim 28, wherein the structural protein is selected from the group consisting of a C protein of dengue-1 virus, a C protein of dengue-2 virus, a C protein of dengue-3 virus, a C protein of dengue-4 virus, a prM protein of dengue-1 virus, a prM protein of dengue-2 virus, a prM protein of dengue-3 virus, a prM protein of dengue-4 virus, an E protein of dengue-1 virus, an E protein of dengue-2 virus, an E protein of dengue-3 virus, an E protein of dengue-3 virus containing a leucine at amino acid position 345, an E protein of dengue-4 virus, an E protein of dengue-4 virus containing a leucine at amino acid position 447, an E protein of dengue-4 virus containing a leucine at amino acid position 447 and a valine at amino acid position 364, a C protein of dengue-2 virus containing a serine at amino acid position 100 or any combination thereof.

31. The nucleic acid chimera of claim 28, wherein the at least two different flaviviruses are selected from the group consisting of the dengue-1 virus, dengue-2 virus, dengue-3 virus, dengue-4 virus, West Nile virus, Japanese encephalitis virus, St. Louis encephalitis virus, tick-borne encephalitis virus, yellow fever virus or any combination thereof.

32. A composition comprising one or more than one nucleic acid chimera of claim 1 and a pharmaceutically acceptable carrier.

33. The composition of claim 32, further comprising an immunizing composition selected from the group consisting of a dengue virus vaccine, a yellow fever virus vaccine, a tick-borne encephalitis virus vaccine, a Japanese encephalitis virus vaccine, a West Nile virus vaccine, a hepatitis C virus vaccine or any combination thereof.

34. A composition comprising one or more than one nucleic acid chimera of claim 28 and a pharmaceutically acceptable carrier.

35. The composition of claim 34, further comprising an immunizing composition selected from the group consisting of a dengue virus vaccine, a yellow fever virus vaccine, a tick-borne encephalitis virus vaccine, a Japanese encephalitis virus vaccine, a West Nile virus vaccine, a hepatitis C virus vaccine or any combination thereof.

36. A method of inducing an immune response in a subject comprising administering an effective amount of the composition of claim 32 to the subject.

37. A method of inducing an immune response in a subject comprising administering an effective amount of the composition of claim 33 to the subject.

38. A method of inducing an immune response in a subject comprising administering an effective amount of the composition of claim 34 to the subject.

39. A method of inducing an immune response in a subject comprising administering an effective amount of the composition of claim 35 to the subject.

40. An isolated nucleic acid consisting essentially of a nucleotide sequence of a genome of a dengue-2 virus, wherein the nucleotide sequence contains a mutation at position 2579 which results in the presence of an aspartate at amino acid residue 53 of the NS1 protein.

41. The nucleic acid of claim 40, wherein the nucleotide sequence further contains a mutation at position 57 which disrupts the function of the 5' noncoding region.

42. The nucleic acid of claim 40, wherein the nucleotide sequence further contains a mutation at position 5270 which results in the presence of a valine at amino acid residue 250 of the NS3 protein.

43. The nucleic acid of claim 42, wherein the nucleotide sequence further contains a mutation at position 57 which disrupts the function of the 5' noncoding region.

44. A nucleic acid chimera comprising the nucleotide sequence of claim 40 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-1 virus, a prM protein of dengue-1 virus, an E protein of dengue-1 virus or any combination thereof.

45. A nucleic acid chimera comprising the nucleotide sequence of claim 40 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-2 virus, a prM protein of dengue-2 virus, an E protein of dengue-2 virus or any combination thereof.

46. A nucleic acid chimera comprising the nucleotide sequence of claim 40 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-3 virus, a prM protein of dengue-3 virus, an E protein of dengue-3 virus or any combination thereof.

47. A nucleic acid chimera comprising the nucleotide sequence of claim 40 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-4 virus, a prM protein of dengue-4 virus, an E protein of dengue-4 virus or any combination thereof.

48. A nucleic acid chimera comprising the nucleotide sequence of claim 41 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-1 virus, a prM protein of dengue-1 virus, an E protein of dengue-1 virus or any combination thereof.

49. A nucleic acid chimera comprising the nucleotide sequence of claim 41 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-2 virus, a prM protein of dengue-2 virus, an E protein of dengue-2 virus or any combination thereof.

50. A nucleic acid chimera comprising the nucleotide sequence of claim 41 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-3 virus, a prM protein of dengue-3 virus, an E protein of dengue-3 virus or any combination thereof.

51. A nucleic acid chimera comprising the nucleotide sequence of claim 41 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-4 virus, a prM protein of dengue-4 virus, an E protein of dengue-4 virus or any combination thereof.

52. A nucleic acid chimera comprising the nucleotide sequence of claim 42 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-1 virus, a prM protein of dengue-1 virus, an E protein of dengue-1 virus or any combination thereof.

53. A nucleic acid chimera comprising the nucleotide sequence of claim 42 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-2 virus, a prM protein of dengue-2 virus, an E protein of dengue-2 virus or any combination thereof.

54. A nucleic acid chimera comprising the nucleotide sequence of claim 42 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-3 virus, a prM protein of dengue-3 virus, an E protein of dengue-3 virus or any combination thereof.

55. A nucleic acid chimera comprising the nucleotide sequence of claim 42 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-4 virus, a prM protein of dengue-4 virus, an E protein of dengue-4 virus or any combination thereof.

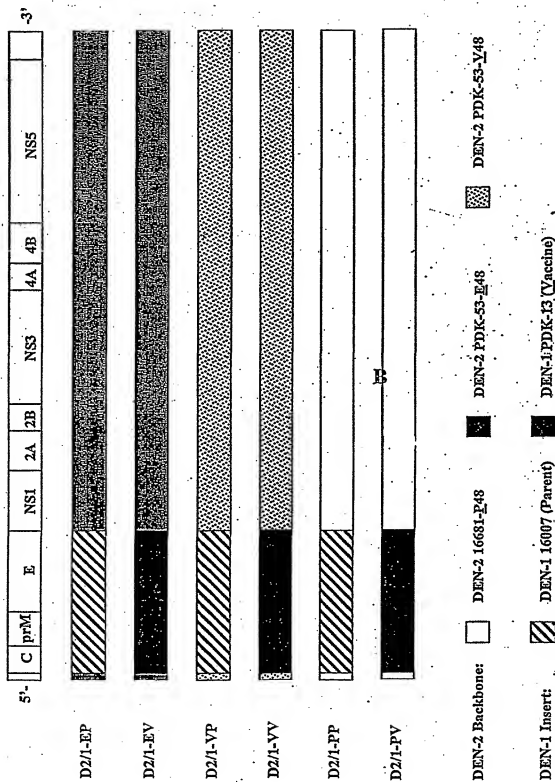
56. A nucleic acid chimera comprising the nucleotide sequence of claim 43 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-1 virus, a prM protein of dengue-1 virus, an E protein of dengue-1 virus or any combination thereof.

57. A nucleic acid chimera comprising the nucleotide sequence of claim 43 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-2 virus, a prM protein of dengue-2 virus, an E protein of dengue-2 virus or any combination thereof.

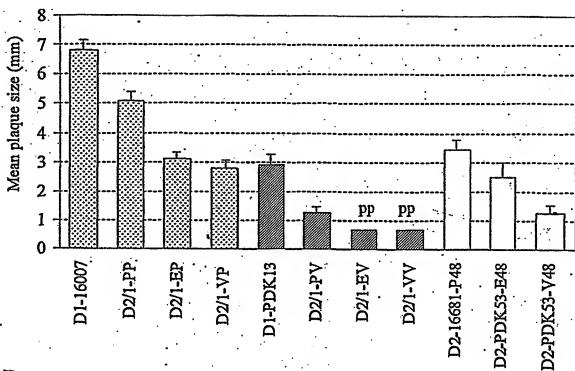
58. A nucleic acid chimera comprising the nucleotide sequence of claim 43 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-3 virus, a prM protein of dengue-3 virus, an E protein of dengue-3 virus or any combination thereof.

59. A nucleic acid chimera comprising the nucleotide sequence of claim 43 and a nucleotide sequence encoding a flavivirus structural protein selected from the group consisting of a C protein of dengue-4 virus, a prM protein of dengue-4 virus, an E protein of dengue-4 virus or any combination thereof.

FIGURE 1



A



B

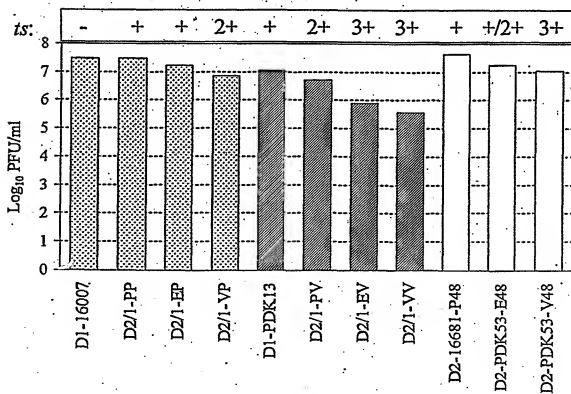


FIGURE 2

FIGURE 3

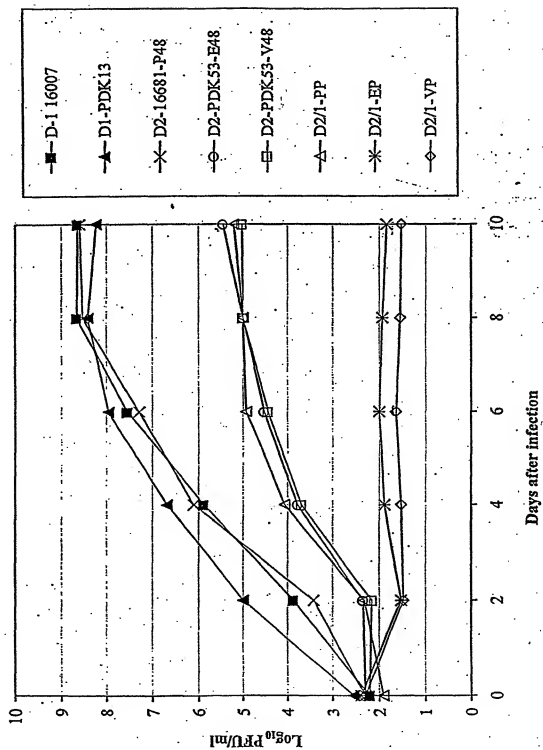
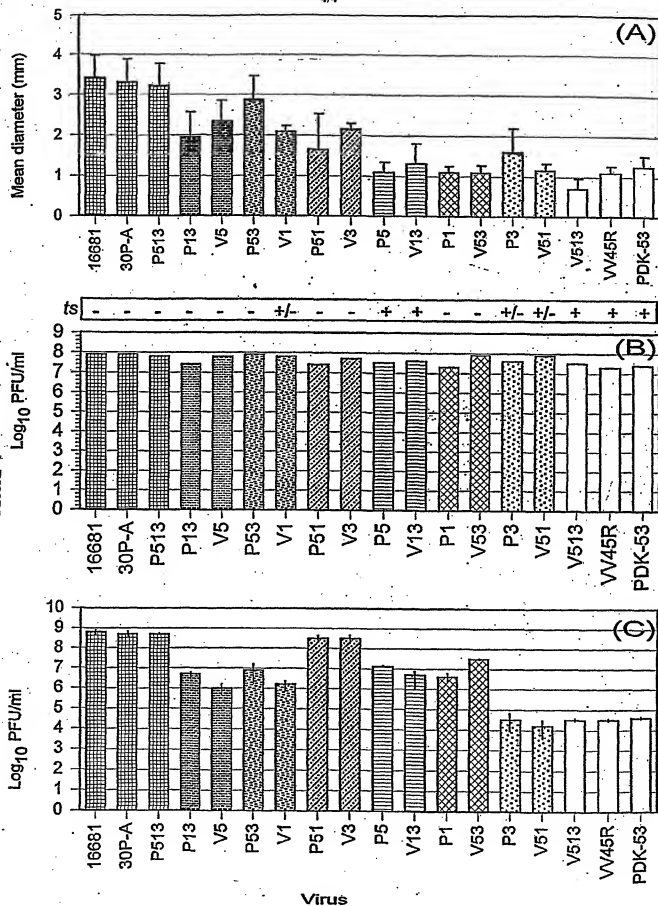


FIGURE 4



SEQUENCE LISTING

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FLAVIVIRUS CHIMERAS

<130> 14114.0334P1

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synthetic construct

<221> CDS

<222> (95)...(10273)

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Met Ile Asn Gln Arg Lys Lys	
1 5	

acg ggt cga ccg tct ttc aat atg ctg aaa cgc gcg aga aac cgc gtg	163
Thr Gly Arg Pro Ser Phe Asn Met Leu Lys Arg Ala Arg Asn Arg Val	
10 15 20	

tca act gtt tca cag ttg gcg aag aga ttc tca aaa gga ttg ctc tca	211
Ser Thr Val Ser Gln Leu Ala Lys Arg Phe Ser Lys Gly Leu Leu Ser	
25 30 35	

ggc caa gga ccc atg aaa ttg gtg atg gct ttc ata gca ttc tta aga	259
Gly Gln Gly Pro Met Lys Leu Val Met Ala Phe Ile Ala Phe Leu Arg	
40 45 50 55	

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Phe Leu Ala Ile Pro Pro Thr Ala Gly Ile Leu Ala Arg Trp Gly Ser	
60 65 70	

2

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75 80 85	
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Ile Ser Asn Met Leu Asn Ile Met Asn Arg Arg Lys Arg Ser Val Thr	
90 95 100	
atg ctg ctt atg ctg ctg ccc aca gcc ctg gcg ttc cat ctg acg aca	451
Met Leu Leu Met Leu Leu Pro Thr Ala Leu Ala Phe His Leu Thr Thr	
105 110 115	
cga ggg gga gag ccg cat atg ata gtt agc aag cag gaa aga gga aag	499
Arg Gly Gly Glu Pro His Met Ile Val Ser Lys Gln Glu Arg Gly Lys	
120 125 130 135	
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Ser Leu Leu Phe Lys Thr Ser Ala Gly Val Asn Met Cys Thr Leu Ile	
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His Arg Arg Asp Lys Arg Ser Val Ala Leu Ala Pro His Val Gly Leu	
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Gly Leu Glu Thr Arg Ala Glu Thr Trp Met Ser Ser Glu Gly Ala Trp	
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Lys Gln Ile Gln Lys Val Glu Thr Trp Ala Leu Arg His Pro Gly Phe	
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Thr Val Ile Ala Leu Phe Leu Ala His Ala Ile Gly Thr Ser Ile Thr	
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atg gga aaa ctg gta cac cag gtt ttt gga act gca tat gga gtt ttg Met Gly Lys Leu Val His Gln Val Phe Gly Thr Ala Tyr Gly Val Leu 715 720 725	2275

ttt agc gga gtt tct tgg acc atg aaa ata gga ata ggg att ctg ctg	2323
Phe Ser Gly Val Ser Trp Thr Met Lys Ile Gly Ile Gly Ile Leu Leu	
730 735 740	
aca tgg cta gga tta aat tca agg aac acg tcc ctt tcg atg atg tgc	2371
Thr Trp Leu Gly Leu Asn Ser Arg Asn Thr Ser Leu Ser Met Met Cys	
745 750 755	
atc gca gtt ggc atg gtc aca ctg tac cta gga gtc atg gtt cag gca	2419
Ile Ala Val Gly Met Val Thr Leu Tyr Leu Gly Val Met Val Gln Ala	
760 765 770 775	
gat tcg gga tgt gta atc aac tgg aaa ggc aga gaa ctt aaa tgt gga	2467
Asp Ser Gly Cys Val Ile Asn Trp Lys Gly Arg Glu Leu Lys Cys Gly	
780 785 790	
agc ggc att ttt gtc act aat gaa gtt cac act tgg aca gag caa tac	2515
Ser Gly Ile Phe Val Thr Asn Glu Val His Thr Trp Thr Glu Gln Tyr	
795 800 805	
aaa ttc cag gct gac tcc ccc aag aga cta tca gca gcc att ggg aag	2563
Lys Phe Gln Ala Asp Ser Pro Lys Arg Leu Ser Ala Ala Ile Gly Lys	
810 815 820	
gca tgg gag gag ggt gtg tgt gga atc cga tca gcc act cgt ctc gag	2611
Ala Trp Glu Glu Gly Val Cys Gly Ile Arg Ser Ala Thr Arg Leu Glu	
825 830 835	
aac atc atg tgg aaa caa ata tca aat gaa ttg aac cac atc cta ctt	2659
Asn Ile Met Trp Lys Gln Ile Ser Asn Glu Leu Asn His Ile Leu Leu	
840 845 850 855	
gaa aat gac atg aaa ttt aca gtg gtc gtg gga gat gtt agt gga atc	2707
Glu Asn Asp Met Lys Phe Thr Val Val Val Gly Asp Val Ser Gly Ile	
860 865 870	
ttg gcc caa ggg aaa aaa atg att agg cca caa ccc atg gaa cac aaa	2755
Leu Ala Gln Gly Lys Lys Met Ile Arg Pro Gln Pro Met Glu His Lys	
875 880 885	
tac tcg tgg aaa agc tgg gga aaa gcc aaa atc ata gga gcg gat gta	2803
Tyr Ser Trp Lys Ser Trp Gly Lys Ala Lys Ile Ile Gly Ala Asp Val	
890 895 900	
cag aac acc acc ttc atc atc gac ggc cca aac acc cca gaa tgc cct	2851
Gln Asn Thr Thr Phe Ile Ile Asp Gly Pro Asn Thr Pro Glu Cys Pro	
905 910 915	
gac aat caa aga gca tgg aat att tgg gaa gta gag gac tat gga ttt	2899
Asp Asn Gln Arg Ala Trp Asn Ile Trp Glu Val Glu Asp Tyr Gly Phe	
920 925 930 935	

ggg att ttc acg aca aac ata tgg ttg aaa ttg cgt gac tcc tac acc Gly Ile Phe Thr Thr Asn Ile Trp Leu Lys Leu Arg Asp Ser Tyr Thr	2947
940 945 950	
caa gta tgt gac cac cgg ctg atg tca gct gcc att aag gac agc aag Gln Val Cys Asp His Arg Leu Met Ser Ala Ala Ile Lys Asp Ser Lys	2995
955 960 965	
gca gtc cat gct gac atg ggg tac tgg ata gaa agt gaa aag aac gag Ala Val His Ala Asp Met Gly Tyr Trp Ile Glu Ser Glu Lys Asn Glu	3043
970 975 980	
aca tgg aag ttg gcg aga gcc tcc ttt ata gaa gtt aag aca tgc atc Thr Trp Lys Leu Ala Arg Ala Ser Phe Ile Glu Val Lys Thr Cys Ile	3091
985 990 995	
tgg cca aaa tcc cac act cta tgg agc aat gga gtt ctg gaa agt gaa Trp Pro Lys Ser His Thr Leu Trp Ser Asn Gly Val Leu Glu Ser Glu	3139
1000 1005 1010 1015	
atg ata att cca aag ata tat gga gga cca ata tct cag cac aac tac Met Ile Ile Pro Lys Ile Tyr Gly Gly Pro Ile Ser Gln His Asn Tyr	3187
1020 1025 1030	
aga cca gga tat ttc aca caa aca gca ggg ccg tgg cac cta ggc aag Arg Pro Gly Tyr Phe Thr Gln Thr Ala Gly Pro Trp His Leu Gly Lys	3235
1035 1040 1045	
ttg gaa cta gat ttc gat ttt tgt gaa ggt acc aca gtt gtt gtg gat Leu Glu Leu Asp Phe Asp Phe Cys Glu Gly Thr Thr Val Val Val Asp	3283
1050 1055 1060	
gaa cat tgt gga aat cga gga cca tct ctc aga acc aca aca gtc aca Glu His Cys Gly Asn Arg Gly Pro Ser Leu Arg Thr Thr Thr Val Thr	3331
1065 1070 1075	
gga aag ata atc cat gaa tgg tgc tgc aga tct tgt acg cta ccc ccc Gly Lys Ile Ile His Glu Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro	3379
1080 1085 1090 1095	
cta cgt ttc aaa ggg gaa gac ggg tgt tgg tac ggc atg gaa atc aga Leu Arg Phe Lys Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg	3427
1100 1105 1110	
cca gtg aag gac aag gaa gag aac ctg gtc aag tca atg gtc tct gca Pro Val Lys Asp Lys Glu Glu Asn Leu Val Lys Ser Met Val Ser Ala	3475
1115 1120 1125	
ggg tca gga gaa gtg gac agc ttt tca cta gga ctg cta tgc ata tca Gly Ser Gly Glu Val Asp Ser Phe Ser Leu Gly Leu Leu Cys Ile Ser	3523
1130 1135 1140	
ata atg att gaa gaa gtg atg aga tcc aga tgg agc aaa aaa atg ctg Ile Met Ile Glu Glu Val Met Arg Ser Arg Trp Ser Lys Lys Met Leu	3571
1145 1150 1155	

atg act gga aca ctg gct gtg ttc ctc ctt ctt ata atg gga caa ttg Met Thr Gly Thr Leu Ala Val Phe Leu Leu Ile Met Gly Gln Leu 1160 1165 1170 1175	3619
aca tgg agt gat ctg atc agg tta tgt att atg gtt gga gcc aac gct Thr Trp Ser Asp Leu Ile Arg Leu Cys Ile Met Val Gly Ala Asn Ala 1180 1185 1190	3667
tca gac aag atg ggg atg gga aca acg tac cta gct tta atg gcc act Ser Asp Lys Met Gly Met Gly Thr Thr Tyr Leu Ala Leu Met Ala Thr 1195 1200 1205	3715
ttc aaa atg aga cca atg ttc gcc gtc ggg cta tta ttt cgc aga cta Phe Lys Met Arg Pro Met Phe Ala Val Gly Leu Leu Phe Arg Arg Leu 1210 1215 1220	3763
aca tct aga gaa gtt ctt ctt ctt aca att ggc ttg agc ctg gtg gca Thr Ser Arg Glu Val Leu Leu Leu Thr Ile Gly Leu Ser Leu Val Ala 1225 1230 1235	3811
tcc gtg gag cta cca agt tcc cta gag gag ctg ggg gat gga ctt gca Ser Val Glu Leu Pro Ser Ser Leu Glu Glu Leu Gly Asp Gly Leu Ala 1240 1245 1250 1255	3859
ata ggc atc atg atg ttg aaa tta ttg act gat ttt cag tca cac cag Ile Gly Ile Met Met Leu Lys Leu Leu Thr Asp Phe Gln Ser His Gln 1260 1265 1270	3907
cta tgg gct act ctg cta tcc ttg aca ttt att aaa aca act ttt tca Leu Trp Ala Thr Leu Leu Ser Leu Thr Phe Ile Lys Thr Thr Phe Ser 1275 1280 1285	3955
ttg cac tat gca tgg aag aca atg gct atg gta ctg tca att gta tct Leu His Tyr Ala Trp Lys Thr Met Ala Met Val Leu Ser Ile Val Ser 1290 1295 1300	4003
ctc ttc cct tta tgc ctg tcc acg acc tct caa aaa aca aca tgg ctt Leu Phe Pro Leu Cys Leu Ser Thr Thr Ser Gln Lys Thr Thr Trp Leu 1305 1310 1315	4051
cgg gtg ctg ttg gga tct ctt gga tgc aaa cca cta ccc atg ttt ctt Pro Val Leu Leu Gly Ser Leu Gly Cys Lys Pro Leu Pro Met Phe Leu 1320 1325 1330 1335	4099
ata aca gaa aac aaa atc tgg gga agg aag agt tgg ccc ctc aat gaa Ile Thr Glu Asn Lys Ile Trp Gly Arg Lys Ser Trp Pro Leu Asn Glu 1340 1345 1350	4147
gga att atg gct gtt gga ata gtt agt att cta cta agt tca ctt tta Gly Ile Met Ala Val Gly Ile Val Ser Ile Leu Leu Ser Ser Leu Leu 1355 1360 1365	4195

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aaa gcg gct gag gtc tcc tgg gag gaa gaa gca gaa cac tca ggc gcc Lys Ala Ala Glu Val Ser Trp Glu Glu Glu Ala Glu His Ser Gly Ala 1400 1405 1410 1415	4339
tca cac aac ata cta gta gag gtt caa gat gat gga acc atg aag ata Ser His Asn Ile Leu Val Glu Val Gln Asp Asp Gly Thr Met Lys Ile 1420 1425 1430	4387
aaa gat gaa gag aga gat gac acg ctc acc att ctc ctt aaa gca act Lys Asp Glu Glu Arg Asp Asp Thr Leu Thr Ile Leu Leu Lys Ala Thr 1435 1440 1445	4435
ctg ctg gca gtc tca ggg gtg tac cca atg tca ata cca gcg acc ctt Leu Leu Ala Val Ser Gly Val Tyr Pro Met Ser Ile Pro Ala Thr Leu 1450 1455 1460	4483
ttt gtg tgg tat ttt tgg cag aaa aag aaa cag aga tca gga gtg cta Phe Val Trp Tyr Phe Trp Gln Lys Lys Lys Gln Arg Ser Gly Val Leu 1465 1470 1475	4531
tgg gac aca ccc agc ccc cca gaa gtg gaa aga gca gtt ctt gat gat Trp Asp Thr Pro Ser Pro Pro Glu Val Glu Arg Ala Val Leu Asp Asp 1480 1485 1490 1495	4579
ggc atc tat aga att ttg caa aga gga ctg ttg ggc agg tcc caa gta Gly Ile Tyr Arg Ile Leu Gln Arg Gly Leu Leu Gly Arg Ser Gln Val 1500 1505 1510	4627
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act agg gga gct gtc ctc atg tat caa gga aaa agg ctg gaa cca agc Thr Arg Gly Ala Val Leu Met Tyr Gln Gly Lys Arg Leu Glu Pro Ser 1530 1535 1540	4723
tgg gcc agt gtc aaa aaa gac ttg atc tca tat gga gga ggt tgg agg Trp Ala Ser Val Lys Lys Asp Leu Ile Ser Tyr Gly Gly Gly Trp Arg 1545 1550 1555	4771
ttt caa gga tcc tgg aac acg gga gaa gaa gta cag gtg att gct gtt Phe Gln Gly Ser Trp Asn Thr Gly Glu Glu Val Gln Val Ile Ala Val 1560 1565 1570 1575	4819
gaa ccg gga aaa aac ccc aaa aat gta caa aca acg ccg ggt acc ttc Glu Pro Gly Lys Asn Pro Lys Asn Val Gln Thr Thr Pro Gly Thr Phe 1580 1585 1590	4867

aag acc cct gaa ggc gaa gtt gga gcc ata gcc tta gac ttt aaa cct Lys Thr Pro Glu Gly Glu Val Gly Ala Ile Ala Leu Asp Phe Lys Pro 1595 1600 1605	4915
ggc acc tct gga tct ccc atc gta aac aga gag gga aaa ata gta ggt Gly Thr Ser Gly Ser Pro Ile Val Asn Arg Glu Gly Lys Ile Val Gly 1610 1615 1620	4963
ctt tat gga aat gga gtg gtg aca aca agc gga act tac gtt agt gcc Leu Tyr Gly Asn Gly Val Val Thr Thr Ser Gly Thr Tyr Val Ser Ala 1625 1630 1635	5011
ata gct caa gct aag gca tca caa gaa ggg cct cta cca gag att gag Ile Ala Gln Ala Lys Ala Ser Gln Glu Gly Pro Leu Pro Glu Ile Glu 1640 1645 1650 1655	5059
gac gag gtg ttt agg aaa aga aac tta aca ata atg gac cta cat cca Asp Glu Val Phe Arg Lys Arg Asn Leu Thr Ile Met Asp Leu His Pro 1660 1665 1670	5107
gga tcg gga aaa aca aga aga tac ctt cca gcc ata gtc cgt gag gcc Gly Ser Gly Lys Thr Arg Arg Tyr Leu Pro Ala Ile Val Arg Glu Ala 1675 1680 1685	5155
ata aaa agg aag ctg cgc acg cta atc cta gct ccc aca aga gtt gtc Ile Lys Arg Lys Leu Arg Thr Leu Ile Leu Ala Pro Thr Arg Val Val 1690 1695 1700	5203
gct tct gaa atg gca gag gca ctc aag gga gtg cca ata agg tat cag Ala Ser Glu Met Ala Glu Ala Leu Lys Gly Val Pro Ile Arg Tyr Gln 1705 1710 1715	5251
aca aca gca gtg aag agt gaa cac aca gga aag gag ata gtt gac ctt Thr Thr Ala Val Lys Ser Glu His Thr Gly Lys Glu Ile Val Asp Leu 1720 1725 1730 1735	5299
atg tgc cac gcc act ttc acc atg cgc ctc ctg tct ccc gtg aga gtt Met Cys His Ala Thr Phe Thr Met Arg Leu Leu Ser Pro Val Arg Val 1740 1745 1750	5347
ccc aat tat aac atg att atc atg gat gaa gca cac ttc acc gat cca Pro Asn Tyr Asn Met Ile Ile Met Asp Glu Ala His Phe Thr Asp Pro 1755 1760 1765	5395
gcc agc ata gca gcc aga ggg tac atc tca acc cga gtg ggt atg ggt Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Gly Met Gly 1770 1775 1780	5443
gaa gca gct gcg atc ttt atg aca gcc act ccc cca gga tcg gtg gag Glu Ala Ala Ala Ile Phe Met Thr Ala Thr Pro Pro Gly Ser Val Glu 1785 1790 1795	5491

gcc ttt cca cag agc aat gca att atc caa gat gag gaa aga gac att Ala Phe Pro Gln Ser Asn Ala Ile Ile Gln Asp Glu Glu Arg Asp Ile 1800 1805 1810 1815	5539
cct gag aga tca tgg aac tca ggc tat gac tgg atc act gat ttt cca Pro Glu Arg Ser Trp Asn Ser Gly Tyr Asp Trp Ile Thr Asp Phe Pro 1820 1825 1830	5587
ggc aaa aca gtc tgg ttt gtt cca agc atc aaa tca gga aat gac att Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys Ser Gly Asn Asp Ile 1835 1840 1845	5635
gcc aac tgt tta aga aaa aac ggg aaa cgg gtg atc caa ttg agc aga Ala Asn Cys Leu Arg Lys Asn Gly Lys Arg Val Ile Gln Leu Ser Arg 1850 1855 1860	5683
aaa acc ttt gac act gag tac cag aaa aca aaa aac aac gac tgg gac Lys Thr Phe Asp Thr Glu Tyr Gln Lys Thr Lys Asn Asn Asp Trp Asp 1865 1870 1875	5731
tat gtc gtc aca aca gac att tcc gaa atg gga gca aat ttc cgg gcc Tyr Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Arg Ala 1880 1885 1890 1895	5779
gac agg gta ata gac cca agg cgg tgt ctg aaa ccg gta ata cta aaa Asp Arg Val Ile Asp Pro Arg Arg Cys Leu Lys Pro Val Ile Leu Lys 1900 1905 1910	5827
gat ggt cca gag cgc gtc att cta gcc gga ccg atg cca gtg act gtg Asp Gly Pro Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr Val 1915 1920 1925	5875
gcc agt gcc gcc cag agg aga gga aga att gga agg aac caa aac aag Ala Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Gln Asn Lys 1930 1935 1940	5923
gaa ggt gat cag tat att tac atg gga cag cct tta aac aat gat gag Glu Gly Asp Gln Tyr Ile Tyr Met Gly Gln Pro Leu Asn Asn Asp Glu 1945 1950 1955	5971
gac cac gct cat tgg aca gaa gca aag atg ctc ctt gac aat ata aac Asp His Ala His Trp Thr Glu Ala Lys Met Leu Leu Asp Asn Ile Asn 1960 1965 1970 1975	6019
aca cca gaa ggg att atc cca gcc ctc tat gag ccg gag aga gaa aag Thr Pro Glu Gly Ile Ile Pro Ala Leu Tyr Glu Pro Glu Arg Glu Lys 1980 1985 1990	6067
agt gca gct ata gac ggg gaa tac aga ctg cgg ggt gaa gca agg aaa Ser Ala Ala Ile Asp Gly Glu Tyr Arg Leu Arg Gly Glu Ala Arg Lys 1995 2000 2005	6115
acg ttc gtg gag ctc atg aga aga ggg gat cta cca gtc tgg cta tcc Thr Phe Val Glu Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ser 2010 2015 2020	6163

tac aaa gtt gcc tca gaa ggc ttc cag tac tcc gac aga agg tgg tgc Tyr Lys Val Ala Ser Glu Gly Phe Gln Tyr Ser Asp Arg Arg Trp Cys 2025 2030 2035	6211
ttc gat ggg gaa agg aac aac cag gtg ttg gag gag aac atg gac gtg Phe Asp Gly Glu Arg Asn Asn Gln Val Leu Glu Glu Asn Met Asp Val 2040 2045 2050 2055	6259
gag atc tgg aca aaa gaa gga gaa aga aag aaa cta cga cct cgc tgg Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys Lys Leu Arg Pro Arg Trp 2060 2065 2070	6307
ttg gac gcc aga aca tac tct gac cca ctg gct ctg cgc gag ttt aaa Leu Asp Ala Arg Thr Tyr Ser Asp Pro Leu Ala Leu Arg Glu Phe Lys 2075 2080 2085	6355
gag ttt gca gca gga aga aga agc gtc tca ggt gac cta ata tta gaa Glu Phe Ala Ala Gly Arg Arg Ser Val Ser Gly Asp Leu Ile Leu Glu 2090 2095 2100	6403
ata ggg aaa ctt cca caa cat ttg acg caa agg gcc cag aat gct ttg Ile Gly Lys Leu Pro Gln His Leu Thr Gln Arg Ala Gln Asn Ala Leu 2105 2110 2115	6451
gac aac ttg gtc atg ttg cac aat tcc gaa caa gga gga aaa gcc tat Asp Asn Leu Val Met Leu His Asn Ser Glu Gln Gly Lys Ala Tyr 2120 2125 2130 2135	6499
aga cat gct atg gaa gaa ctg cca gac aca ata gaa acg ttg atg ctc Arg His Ala Met Glu Glu Leu Pro Asp Thr Ile Glu Thr Leu Met Leu 2140 2145 2150	6547
cta gcc ttg ata gct gtg ttg act ggt gga gtg acg ctg ttc ttc cta Leu Ala Leu Ile Ala Val Leu Thr Gly Gly Val Thr Leu Phe Phe Leu 2155 2160 2165	6595
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gcc tca agc gca ctg tta tgg atg gcc agt gtg gag ccc cat tgg ata Ala Ser Ser Ala Leu Leu Trp Met Ala Ser Val Glu Pro His Trp Ile 2185 2190 2195	6691
gcg gcc tcc atc ata ctg gag ttc ttt ctg atg gta ctg ctt att cca Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Met Val Leu Leu Ile Pro 2200 2205 2210 2215	6739
gag cca gac aga cag cgc act cca cag gac aac cag cta gca tat gtg Glu Pro Asp Arg Gln Arg Thr Pro Gln Asp Asn Gln Leu Ala Tyr Val 2220 2225 2230	6787

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gtg ata ggt ctg tta ttc atg ata ttg aca gtg gca gcc aat gag atg Val Ile Gly Leu Leu Phe Met Ile Leu Thr Val Ala Ala Asn Glu Met 2235 2240 2245	6835
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gct gaa aac cac cac cat gct aca atg ctg gac gta gac cta cat cca Ala Glu Asn His His His Ala Thr Met Leu Asp Val Asp Leu His Pro 2265 2270 2275	6931
gct tca gcc tgg acc ctc tat gca gtg gcc aca aca atc atc act cct Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Ile Ile Thr Pro 2280 2285 2290 2295	6979
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cca ata tog aag atg gac ata gga gtt cca ctt ctc gcc ttg ggg tgc Pro Ile Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala Leu Gly Cys 2330 2335 2340	7123
tat tcc caa gtg aat ccg ctg aca ctg ata gcg gca gta ttg atg cta Tyr Ser Gln Val Asn Pro Leu Thr Leu Ile Ala Ala Val Leu Met Leu 2345 2350 2355	7171
gta gct cat tac gcc ata att gga cct gga ctg caa gca aaa gct act Val Ala His Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr 2360 2365 2370 2375	7219
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tca cag att ctt ttg atg cgg act aca tgg gcc ttg tgt gaa tcc atc Ser Gln Ile Leu Leu Met Arg Thr Thr Trp Ala Leu Cys Glu Ser Ile 2425 2430 2435	7411
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ggg agt tat cta gca gga gca ggt ctg gcc ttc tca tta atg aaa tct Gly Ser Tyr Leu Ala Gly Ala Gly Leu Ala Phe Ser Leu Met Lys Ser 2475 2480 2485	7555
cta gga gga ggt agg aga ggc acg gga gcc caa ggg gaa aca ctg gga Leu Gly Gly Gly Arg Arg Gly Thr Gly Ala Gln Gly Glu Thr Leu Gly 2490 2495 2500	7603
gaa aaa tgg aaa aga caa cta aac caa ctg agc aag tca gaa ttc aat Glu Lys Trp Lys Arg Gln Leu Asn Gln Leu Ser Lys Ser Glu Phe Asn 2505 2510 2515	7651
act tac aag agg agt ggg att atg gag gtg gat aga tcc gaa gcc aaa Thr Tyr Lys Arg Ser Gly Ile Met Glu Val Asp Arg Ser Glu Ala Lys 2520 2525 2530 2535	7699
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acg gcc aaa ctg agg tgg ttc gtg gag agg aac ctt gtg aaa cca gaa Thr Ala Lys Leu Arg Trp Phe Val Glu Arg Asn Leu Val Lys Pro Glu 2555 2560 2565	7795
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cta gta aag ctg cac tcc gga aaa gat gta ttt ttt ata cca cct gag Leu Val Lys Leu His Ser Gly Lys Asp Val Phe Phe Ile Pro Pro Glu 2620 2625 2630	7987
aaa tgt gac acc ctt ttg tgt gat att ggt gag tcc tct ccg aac cca Lys Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro 2635 2640 2645	8035
act ata gag gaa gga aga acg tta cgt gtt ctg aaa atg gtg gaa cca Thr Ile Glu Glu Gly Arg Thr Leu Arg Val Leu Lys Met Val Glu Pro 2650 2655 2660	8083

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tgg ctc aga gga aac caa ttt tgc ata aaa att cta aat ccc tat atg Trp Leu Arg Gly Asn Gln Phe Cys Ile Lys Ile Leu Asn Pro Tyr Met 2665 2670 2675	8131
ccg agc gtg gta gaa act ctg gaa caa atg caa aga aaa cat gga gga Pro Ser Val Val Glu Thr Leu Glu Gln Met Gln Arg Lys His Gly Gly 2680 2685 2690 2695	8179
atg cta gtg cga aac cca ctc tca aga aat tcc acc cat gaa atg tac Met Leu Val Arg Asn Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr 2700 2705 2710	8227
tgg gtt tca tgt gga aca gga aac att gtg tca gca gta aac atg aca Trp Val Ser Cys Gly Thr Gly Asn Ile Val Ser Ala Val Asn Met Thr 2715 2720 2725	8275
tct aga atg ttg cta aat cgg ttc aca atg gct cac agg aag cca aca Ser Arg Met Leu Leu Asn Arg Phe Thr Met Ala His Arg Lys Pro Thr 2730 2735 2740	8323
tat gaa aga gac gtg gac tta ggc gct gga aca aga cat gtg gca gta Tyr Glu Arg Asp Val Asp Leu Gly Ala Gly Thr Arg His Val Ala Val 2745 2750 2755	8371
gaa cca gag gta gcc aac cta gat atc att ggc cag agg ata gag aat Glu Pro Glu Val Ala Asn Leu Asp Ile Ile Gly Gln Arg Ile Glu Asn 2760 2765 2770 2775	8419
ata aaa aat gaa cat aag tca aca tgg cat tat gat gag gac aat cca Ile Lys Asn Glu His Lys Ser Thr Trp His Tyr Asp Glu Asp Asn Pro 2780 2785 2790	8467
tac aaa aca tgg gcc tat cat gga tca tat gag gtt aag cca tca gga Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Val Lys Pro Ser Gly 2795 2800 2805	8515
tcg gcc tca tcc atg gtc aat ggc gtg gtg aga ttg ctc acc aaa cca Ser Ala Ser Ser Met Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro 2810 2815 2820	8563
tgg gat gtt atc ccc atg gtc aca caa ata gcc atg act gat acc aca Trp Asp Val Ile Pro Met Val Thr Gln Ile Ala Met Thr Asp Thr Thr 2825 2830 2835	8611
ccc ttt gga caa cag agg gtg ttt aaa gag aaa gtt gac acg cgc aca Pro Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr 2840 2845 2850 2855	8659
cca aaa gca aaa cgt ggc aca gca caa att atg gaa gtg aca gcc agg Pro Lys Ala Lys Arg Gly Thr Ala Gln Ile Met Glu Val Thr Ala Arg 2860 2865 2870	8707
tgg tta tgg ggt ttc ctt tct aga aac aaa aaa ccc aga att tgc aca Trp Leu Trp Gly Phe Leu Ser Arg Asn Lys Lys Pro Arg Ile Cys Thr 2875 2880 2885	8755

aga gag gag ttt aca aga aaa gtt agg tca aac gca gct att gga gca Arg Glu Glu Phe Thr Arg Lys Val Arg Ser Asn Ala Ala Ile Gly Ala 2890 2895 2900	8803
gtg ttc gtt gat gaa aat caa tgg aac tcg gca aaa gaa gca gtg gaa Val Phe Val Asp Glu Asn Gln Trp Asn Ser Ala Lys Glu Ala Val Glu 2905 2910 2915	8851
gac gaa cgg ttc tgg gaa ctt gtc cac aga gag agg gag ctt cat aaa Asp Glu Arg Phe Trp Glu Leu Val His Arg Glu Arg Glu Leu His Lys 2920 2925 2930 2935	8899
cag ggg aaa tgt gcc acg tgt gtc tac aat atg atg ggg aag aga gag Gln Gly Lys Cys Ala Thr Cys Val Tyr Asn Met Met Gly Lys Arg Glu 2940 2945 2950	8947
aaa aaa tta gga gag ttc gga aag gca aaa gga agt cgt gca ata tgg Lys Lys Leu Gly Glu Phe Gly Lys Ala Lys Gly Ser Arg Ala Ile Trp 2955 2960 2965	8995
tac atg tgg ttg gga gca cgc ttc cta gag ttt gaa gcc ctt ggt ttc Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu Phe Glu Ala Leu Gly Phe 2970 2975 2980	9043
atg aat gaa gat cac tgg ttc agt aga gag aat tca ctc agt gga gtg Met Asn Glu Asp His Trp Phe Ser Arg Glu Asn Ser Leu Ser Gly Val 2985 2990 2995	9091
gaa gga gaa gga ctc cac aaa ctt gga tac ata ctc aga gac ata tca Glu Gly Glu Gly Leu His Lys Leu Gly Tyr Ile Leu Arg Asp Ile Ser 3000 3005 3010 3015	9139
agg att cca ggg ggg aac atg tat gca gat gac aca gcc gga tgg gac Arg Ile Pro Gly Gly Asn Met Tyr Ala Asp Thr Ala Gly Trp Asp 3020 3025 3030	9187
aca aga ata aca gag gat gat ctc cag aat gag gct aaa atc act gac Thr Arg Ile Thr Glu Asp Asp Leu Gln Asn Glu Ala Lys Ile Thr Asp 3035 3040 3045	9235
atc atg gag ccc gaa cat gcc ctg ctg gct acg tca atc ttt aag ctg Ile Met Glu Pro Glu His Ala Leu Leu Ala Thr Ser Ile Phe Lys Leu 3050 3055 3060	9283
acc tac caa aat aag gtg gta agg gtg cag aga cca gca aaa aat gga Thr Tyr Gln Asn Lys Val Arg Val Gln Arg Pro Ala Lys Asn Gly 3065 3070 3075	9331
acc gtg atg gat gtt ata tcc aga cgt gac cag aga ggc agt gga cag Thr Val Met Asp Val Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly Gln 3080 3085 3090 3095	9379

16

gtt gga act tat ggc tta aac act ttc acc aac atg gag gcc caa ctg Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu 3100 3105 3110	9427
ata aga caa atg gag tcc gag gga atc ttt tta ccc agc gaa ttg gaa Ile Arg Gln Met Glu Ser Glu Gly Ile Phe Leu Pro Ser Glu Leu Glu 3115 3120 3125	9475
acc cca aat cta gcc gga aga gtt ctc gac tgg ttg gaa aaa tat ggt Thr Pro Asn Leu Ala Gly Arg Val Leu Asp Trp Leu Glu Lys Tyr Gly 3130 3135 3140	9523
gtc gaa agg ctg aaa aga atg gca atc agc gga gat gac tgt gtg gtg Val Glu Arg Leu Lys Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val 3145 3150 3155	9571
aaa cca att gat gac agg ttc gca aca gcc tta aca gct ttg aat gac Lys Pro Ile Asp Asp Arg Phe Ala Thr Ala Leu Thr Ala Leu Asn Asp 3160 3165 3170 3175	9619
atg gga aaa gta aga aaa gac ata cca caa tgg gaa cct tca aaa gga Met Gly Lys Val Arg Lys Asp Ile Pro Gln Trp Glu Pro Ser Lys Gly 3180 3185 3190	9667
tgg aat gat tgg caa caa gtg cct ttc tgt tca cac cac ttc cac cag Trp Asn Asp Trp Gln Gln Val Pro Phe Cys Ser His His Phe His Gln 3195 3200 3205	9715
cta att atg aag gat ggg agg gag ata gtg gtg cca tgc cgc aac caa Leu Ile Met Lys Asp Gly Arg Glu Ile Val Val Pro Cys Arg Asn Gln 3210 3215 3220	9763
gat gaa ctt gtg ggg agg gcc aga gta tca caa gcc gcc gga tgg agc Asp Glu Leu Val Gly Arg Ala Arg Val Ser Gln Gly Ala Gly Trp Ser 3225 3230 3235	9811
ctg aga gaa acc gca tgc cta ggc aag tca tat gca caa atg tgg cag Leu Arg Glu Thr Ala Cys Leu Gly Lys Ser Tyr Ala Gln Met Trp Gln 3240 3245 3250 3255	9859
ctg atg tat ttc cac agg aga gac ctg aga ctg gcg gct aac gct att Leu Met Tyr Phe His Arg Arg Asp Leu Arg Leu Ala Ala Asn Ala Ile 3260 3265 3270	9907
tgt tca gcc gtt cca gtt gat tgg gtc cca acc agc cgc acc acc tgg Cys Ser Ala Val Pro Val Asp Trp Val Pro Thr Ser Arg Thr Thr Trp 3275 3280 3285	9955
tcg atc cat gcc cat cac caa tgg atg aca aca gaa gac atg tta tca Ser Ile His Ala His His Gln Trp Met Thr Thr Glu Asp Met Leu Ser 3290 3295 3300	10003
gta tgg aat agg gtc tgg ata gag gaa aac cca tgg atg gag gat aag Val Trp Asn Arg Val Trp Ile Glu Glu Asn Pro Trp Met Glu Asp Lys 3305 3310 3315	10051

17

act cat gtg tcc agt tgg gaa gaa gtt cca tac cta gga aag agg gaa 10099
 Thr His Val Ser Ser Trp Glu Glu Val Pro Tyr Leu Gly Lys Arg Glu
 3320 3325 3330 3335

gat cag tgg tgt gga tcc ctg ata ggc tta aca gca agg gcc acc tgg 10147
 Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ala Arg Ala Thr Trp
 3340 3345 3350

gcc act aat ata caa gtg gcc ata aac caa gtg aga agg ctc att ggg 10195
 Ala Thr Asn Ile Gln Val Ala Ile Asn Gln Val Arg Arg Leu Ile Gly
 3355 3360 3365

aat gag aat tat cta gat tac atg aca tca atg aag aga ttc aag aat 10243
 Asn Glu Asn Tyr Leu Asp Tyr Met Thr Ser Met Lys Arg Phe Lys Asn
 3370 3375 3380

gag agt gat ccc gaa ggg gca ctc tgg taa gtcaacacat tcacaaaata 10293
 Glu Ser Asp Pro Glu Gly Ala Leu Trp *
 3385 3390

aaggaaaata aaaaatcaaa tgaggcaaga agtcaggcca gattaagcca tagtacggta 10353
 agagctatgc tgcctgtgag ccccgcccaa ggacgtaaaa tgaagtacagg ccgaaagcca 10413
 cggtttgagc aagccgtgct gcctgtggct ccacgtggg gatgtaaaaa ccggggaggc 10473
 tgcaacccat ggaagctgta cgcattgggt agcagactag tggttagagg agacccctcc 10533
 caagacacaa cgcagcagcg gggccaaca ccagggggaag ctgtaccctg gtggtaagga 10593
 ctagagggta gaggagaccc ccgcgtaac aataaacagc atattgacgc tgggagagag 10653
 cagagatcct gctgtctcta cagcatcatt ccaggccag aagccagaa aatggaatgg 10713
 tgctgtgaa tcaacagggt ct 10735

<210> 2

<211> 3392

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
 synthetic construct

<400> 2

Met Ile Asn Gln Arg Lys Lys Thr Gly Arg Pro Ser Phe Asn Met Leu
 1 5 10 15
 Lys Arg Ala Arg Asn Arg Val Ser Thr Val Ser Gln Leu Ala Lys Arg
 20 25 30
 Phe Ser Lys Gly Leu Leu Ser Gly Gln Gly Pro Met Lys Leu Val Met
 35 40 45
 Ala Phe Ile Ala Phe Leu Arg Phe Leu Ala Ile Pro Pro Thr Ala Gly
 50 55 60
 Ile Leu Ala Arg Trp Gly Ser Phe Lys Lys Asn Gly Ala Ile Lys Val
 65 70 75 80
 Leu Arg Gly Phe Lys Arg Glu Ile Ser Asn Met Leu Asn Ile Met Asn
 85 90 95
 Arg Arg Lys Arg Ser Val Thr Met Leu Leu Met Leu Leu Pro Thr Ala
 100 105 110

Leu Ala Phe His Leu Thr Thr Arg Gly Gly Glu Pro His Met Ile Val
 115 120 125
 Ser Lys Gln Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ser Ala Gly
 130 135 140
 Val Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Leu Cys Glu
 145 150 155 160
 Asp Thr Met Thr Tyr Lys Cys Pro Arg Ile Thr Glu Ala Glu Pro Asp
 165 170 175
 Asp Val Asp Cys Trp Cys Asn Ala Thr Asp Thr Trp Val Thr Tyr Gly
 180 185 190
 Thr Cys Ser Gln Thr Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala
 195 200 205
 Leu Ala Pro His Val Gly Leu Gly Leu Glu Thr Arg Ala Glu Thr Trp
 210 215 220
 Met Ser Ser Glu Gly Ala Trp Lys Gln Ile Gln Lys Val Glu Thr Trp
 225 230 235 240
 Ala Leu Arg His Pro Gly Phe Thr Val Ile Ala Leu Phe Leu Ala His
 245 250 255
 Ala Ile Gly Thr Ser Ile Thr Gln Lys Gly Ile Ile Phe Ile Leu Leu
 260 265 270
 Met Leu Val Thr Pro Ser Met Ala Met Arg Cys Val Gly Ile Gly Asn
 275 280 285
 Arg Asp Phe Val Glu Gly Leu Ser Gly Ala Thr Trp Val Asp Val Val
 290 295 300
 Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr
 305 310 315 320
 Leu Asp Ile Glu Leu Leu Lys Thr Glu Val Thr Asn Pro Ala Val Leu
 325 330 335
 Arg Lys Leu Cys Ile Glu Ala Lys Ile Ser Asn Thr Thr Thr Asp Ser
 340 345 350
 Arg Cys Pro Thr Gln Gly Glu Ala Thr Leu Val Glu Glu Gln Asp Ala
 355 360 365
 Asn Phe Val Cys Arg Arg Thr Phe Val Asp Arg Gly Trp Gly Asn Gly
 370 375 380
 Cys Gly Leu Phe Gly Lys Gly Ser Leu Ile Thr Cys Ala Lys Phe Lys
 385 390 395 400
 Cys Val Thr Lys Leu Glu Gly Lys Ile Val Gln Tyr Glu Asn Leu Lys
 405 410 415
 Tyr Ser Val Ile Val Thr Val His Thr Gly Asp Gln His Gln Val Gly
 420 425 430
 Asn Glu Thr Thr Glu His Gly Thr Thr Ala Thr Ile Thr Pro Gln Ala
 435 440 445
 Pro Thr Ser Glu Ile Gln Leu Thr Asp Tyr Gly Thr Leu Thr Leu Asp
 450 455 460
 Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Thr
 465 470 475 480
 Met Lys Glu Arg Ser Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu
 485 490 495
 Pro Leu Pro Trp Thr Ser Gly Ala Ser Thr Ser Gln Glu Thr Trp Asn
 500 505 510
 Arg Gln Asp Leu Leu Val Thr Phe Lys Thr Ala His Ala Lys Lys Gln
 515 520 525
 Glu Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu
 530 535 540

Thr Gly Ala Thr Glu Ile Gln Thr Ser Gly Thr Thr Thr Ile Phe Ala
 545 550 555 560
 Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Thr Leu Lys Gly
 565 570 575
 Met Ser Tyr Val Met Cys Thr Gly Ser Phe Lys Leu Glu Lys Glu Val
 580 585 590
 Ala Glu Thr Gln His Gly Thr Val Leu Val Gln Val Lys Tyr Glu Gly
 595 600 605
 Thr Asp Ala Pro Cys Lys Ile Pro Phe Ser Thr Gln Asp Glu Lys Gly
 610 615 620
 Ala Thr Gln Asn Gly Arg Leu Ile Thr Ala Asn Pro Ile Val Thr Asp
 625 630 635 640
 Lys Glu Lys Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Glu Ser
 645 650 655
 Tyr Ile Val Val Gly Ala Gly Glu Lys Ala Leu Lys Leu Ser Trp Phe
 660 665 670
 Lys Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly
 675 680 685
 Ala Arg Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser
 690 695 700
 Ile Gly Gly Val Phe Thr Ser Met Gly Lys Leu Val His Gln Val Phe
 705 710 715 720
 Gly Thr Ala Tyr Gly Val Leu Phe Ser Gly Val Ser Trp Thr Met Lys
 725 730 735
 Ile Gly Ile Gly Ile Leu Leu Thr Trp Leu Gly Leu Asn Ser Arg Asn
 740 745 750
 Thr Ser Leu Ser Met Met Cys Ile Ala Val Gly Met Val Thr Leu Tyr
 755 760 765
 Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Ile Asn Trp Lys
 770 775 780
 Gly Arg Glu Leu Lys Cys Gly Ser Gly Ile Phe Val Thr Asn Glu Val
 785 790 795 800
 His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Ala Asp Ser Pro Lys Arg
 805 810 815
 Leu Ser Ala Ala Ile Gly Lys Ala Trp Glu Glu Gly Val Cys Gly Ile
 820 825 830
 Arg Ser Ala Thr Arg Leu Glu Asn Ile Met Trp Lys Gln Ile Ser Asn
 835 840 845
 Glu Leu Asn His Ile Leu Leu Glu Asn Asp Met Lys Phe Thr Val Val
 850 855 860
 Val Gly Asp Val Ser Gly Ile Leu Ala Gln Gly Lys Lys Met Ile Arg
 865 870 875 880
 Pro Gln Pro Met Glu His Lys Tyr Ser Trp Lys Ser Trp Gly Lys Ala
 885 890 895
 Lys Ile Ile Gly Ala Asp Val Gln Asn Thr Thr Phe Ile Ile Asp Gly
 900 905 910
 Pro Asn Thr Pro Glu Cys Pro Asp Asn Gln Arg Ala Trp Asn Ile Trp
 915 920 925
 Glu Val Glu Asp Tyr Gly Phe Gly Ile Phe Thr Thr Asn Ile Trp Leu
 930 935 940
 Lys Leu Arg Asp Ser Tyr Thr Gln Val Cys Asp His Arg Leu Met Ser
 945 950 955 960
 Ala Ala Ile Lys Asp Ser Lys Ala Val His Ala Asp Met Gly Tyr Trp
 965 970 975

Ile Glu Ser Glu Lys Asn Glu Thr Trp Lys Leu Ala Arg Ala Ser Phe
 980 985 990
 Ile Glu Val Lys Thr Cys Ile Trp Pro Lys Ser His Thr Leu Trp Ser
 995 1000 1005
 Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Ile Tyr Gly Gly
 1010 1015 1020
 Pro Ile Ser Gln His Asn Tyr Arg Pro Gly Tyr Phe Thr Gln Thr Ala
 1025 1030 1035 1040
 Gly Pro Trp His Leu Gly Lys Leu Glu Leu Asp Phe Asp Phe Cys Glu
 1045 1050 1055
 Gly Thr Thr Val Val Val Asp Glu His Cys Gly Asn Arg Gly Pro Ser
 1060 1065 1070
 Leu Arg Thr Thr Thr Val Thr Gly Lys Ile Ile His Glu Trp Cys Cys
 1075 1080 1085
 Arg Ser Cys Thr Leu Pro Pro Leu Arg Phe Lys Gly Glu Asp Gly Cys
 1090 1095 1100
 Trp Tyr Gly Met Glu Ile Arg Pro Val Lys Asp Lys Glu Glu Asn Leu
 1105 1110 1115 1120
 Val Lys Ser Met Val Ser Ala Gly Ser Gly Glu Val Asp Ser Phe Ser
 1125 1130 1135
 Leu Gly Leu Leu Cys Ile Ser Ile Met Ile Glu Glu Val Met Arg Ser
 1140 1145 1150
 Arg Trp Ser Lys Lys Met Leu Met Thr Gly Thr Leu Ala Val Phe Leu
 1155 1160 1165
 Leu Leu Ile Met Gly Gln Leu Thr Trp Ser Asp Leu Ile Arg Leu Cys
 1170 1175 1180
 Ile Met Val Gly Ala Asn Ala Ser Asp Lys Met Gly Met Gly Thr Thr
 1185 1190 1195 1200
 Tyr Leu Ala Leu Met Ala Thr Phe Lys Met Arg Pro Met Phe Ala Val
 1205 1210 1215
 Gly Leu Leu Phe Arg Arg Leu Thr Ser Arg Glu Val Leu Leu Leu Thr
 1220 1225 1230
 Ile Gly Leu Ser Leu Val Ala Ser Val Glu Leu Pro Ser Ser Leu Glu
 1235 1240 1245
 Glu Leu Gly Asp Gly Leu Ala Ile Gly Ile Met Met Leu Lys Leu Leu
 1250 1255 1260
 Thr Asp Phe Gln Ser His Gln Leu Trp Ala Thr Leu Leu Ser Leu Thr
 1265 1270 1275 1280
 Phe Ile Lys Thr Thr Phe Ser Leu His Tyr Ala Trp Lys Thr Met Ala
 1285 1290 1295
 Met Val Leu Ser Ile Val Ser Leu Phe Pro Leu Cys Leu Ser Thr Thr
 1300 1305 1310
 Ser Gln Lys Thr Thr Trp Leu Pro Val Leu Leu Gly Ser Leu Gly Cys
 1315 1320 1325
 Lys Pro Leu Pro Met Phe Leu Ile Thr Glu Asn Lys Ile Trp Gly Arg
 1330 1335 1340
 Lys Ser Trp Pro Leu Asn Glu Gly Ile Met Ala Val Gly Ile Val Ser
 1345 1350 1355 1360
 Ile Leu Leu Ser Ser Leu Leu Lys Asn Asp Val Pro Leu Ala Gly Pro
 1365 1370 1375
 Leu Ile Ala Gly Gly Met Leu Ile Ala Cys Tyr Val Ile Ser Gly Ser
 1380 1385 1390
 Ser Ala Asp Leu Ser Leu Glu Lys Ala Ala Glu Val Ser Trp Glu Glu
 1395 1400 1405

Glu Ala Glu His Ser Gly Ala Ser His Asn Ile Leu Val Glu Val Gln
 1410 1415 1420
 Asp Asp Gly Thr Met Lys Ile Lys Asp Glu Glu Arg Asp Asp Thr Leu
 1425 1430 1435 1440
 Thr Ile Leu Leu Lys Ala Thr Leu Leu Ala Val Ser Gly Val Tyr Pro
 1445 1450 1455
 Met Ser Ile Pro Ala Thr Leu Phe Val Trp Tyr Phe Trp Gln Lys Lys
 1460 1465 1470
 Lys Gln Arg Ser Gly Val Leu Trp Asp Thr Pro Ser Pro Pro Glu Val
 1475 1480 1485
 Glu Arg Ala Val Leu Asp Asp Gly Ile Tyr Arg Ile Leu Gln Arg Gly
 1490 1495 1500
 Leu Leu Gly Arg Ser Gln Val Gly Val Gly Val Phe Gln Glu Gly Val
 1505 1510 1515 1520
 Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu Met Tyr Gln
 1525 1530 1535
 Gly Lys Arg Leu Glu Pro Ser Trp Ala Ser Val Lys Lys Asp Leu Ile
 1540 1545 1550
 Ser Tyr Gly Gly Gly Trp Arg Phe Gln Gly Ser Trp Asn Thr Gly Glu
 1555 1560 1565
 Glu Val Gln Val Ile Ala Val Glu Pro Gly Lys Asn Pro Lys Asn Val
 1570 1575 1580
 Gln Thr Thr Pro Gly Thr Phe Lys Thr Pro Glu Gly Glu Val Gly Ala
 1585 1590 1595 1600
 Ile Ala Leu Asp Phe Lys Pro Gly Thr Ser Gly Ser Pro Ile Val Asn
 1605 1610 1615
 Arg Glu Gly Lys Ile Val Gly Leu Tyr Gly Asn Gly Val Val Thr Thr
 1620 1625 1630
 Ser Gly Thr Tyr Val Ser Ala Ile Ala Gln Ala Lys Ala Ser Gln Glu
 1635 1640 1645
 Gly Pro Leu Pro Glu Ile Glu Asp Glu Val Phe Arg Lys Arg Asn Leu
 1650 1655 1660
 Thr Ile Met Asp Leu His Pro Gly Ser Gly Lys Thr Arg Arg Tyr Leu
 1665 1670 1675 1680
 Pro Ala Ile Val Arg Glu Ala Ile Lys Arg Lys Leu Arg Thr Leu Ile
 1685 1690 1695
 Leu Ala Pro Thr Arg Val Val Ala Ser Glu Met Ala Glu Ala Leu Lys
 1700 1705 1710
 Gly Val Pro Ile Arg Tyr Gln Thr Thr Ala Val Lys Ser Glu His Thr
 1715 1720 1725
 Gly Lys Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg
 1730 1735 1740
 Leu Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Met Ile Ile Met Asp
 1745 1750 1755 1760
 Glu Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly Tyr Ile
 1765 1770 1775
 Ser Thr Arg Val Gly Met Gly Glu Ala Ala Ala Ile Phe Met Thr Ala
 1780 1785 1790
 Thr Pro Pro Gly Ser Val Glu Ala Phe Pro Gln Ser Asn Ala Ile Ile
 1795 1800 1805
 Gln Asp Glu Glu Arg Asp Ile Pro Glu Arg Ser Trp Asn Ser Gly Tyr
 1810 1815 1820
 Asp Trp Ile Thr Asp Phe Pro Gly Lys Thr Val Trp Phe Val Pro Ser
 1825 1830 1835 1840

Ile Lys Ser Gly Asn Asp Ile Ala Asn Cys Leu Arg Lys Asn Gly Lys
 1845 1850 1855
 Arg Val Ile Gln Leu Ser Arg Lys Thr Phe Asp Thr Glu Tyr Gln Lys
 1860 1865 1870
 Thr Lys Asn Asn Asp Trp Asp Tyr Val Val Thr Thr Asp Ile Ser Glu
 1875 1880 1885
 Met Gly Ala Asn Phe Arg Ala Asp Arg Val Ile Asp Pro Arg Arg Cys
 1890 1895 1900
 Leu Lys Pro Val Ile Leu Lys Asp Gly Pro Glu Arg Val Ile Leu Ala
 1905 1910 1915 1920
 Gly Pro Met Pro Val Thr Val Ala Ser Ala Ala Gln Arg Arg Gly Arg
 1925 1930 1935
 Ile Gly Arg Asn Gln Asn Lys Glu Gly Asp Gln Tyr Ile Tyr Met Gly
 1940 1945 1950
 Gln Pro Leu Asn Asn Asp Glu Asp His Ala His Trp Thr Glu Ala Lys
 1955 1960 1965
 Met Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ala Leu
 1970 1975 1980
 Tyr Glu Pro Glu Arg Glu Lys Ser Ala Ala Ile Asp Gly Glu Tyr Arg
 1985 1990 1995 2000
 Leu Arg Gly Glu Ala Arg Lys Thr Phe Val Glu Leu Met Arg Arg Gly
 2005 2010 2015
 Asp Leu Pro Val Trp Leu Ser Tyr Lys Val Ala Ser Glu Gly Phe Gln
 2020 2025 2030
 Tyr Ser Asp Arg Arg Trp Cys Phe Asp Gly Glu Arg Asn Asn Gln Val
 2035 2040 2045
 Leu Glu Glu Asn Met Asp Val Glu Ile Trp Thr Lys Glu Gly Glu Arg
 2050 2055 2060
 Lys Lys Leu Arg Pro Arg Trp Leu Asp Ala Arg Thr Tyr Ser Asp Pro
 2065 2070 2075 2080
 Leu Ala Leu Arg Glu Phe Lys Glu Phe Ala Ala Gly Arg Arg Ser Val
 2085 2090 2095
 Ser Gly Asp Leu Ile Leu Glu Ile Gly Lys Leu Pro Gln His Leu Thr
 2100 2105 2110
 Gln Arg Ala Gln Asn Ala Leu Asp Asn Leu Val Met Leu His Asn Ser
 2115 2120 2125
 Glu Gln Gly Gly Lys Ala Tyr Arg His Ala Met Glu Glu Leu Pro Asp
 2130 2135 2140
 Thr Ile Glu Thr Leu Met Leu Leu Ala Leu Ile Ala Val Leu Thr Gly
 2145 2150 2155 2160
 Gly Val Thr Leu Phe Phe Leu Ser Gly Arg Gly Leu Gly Lys Thr Ser
 2165 2170 2175
 Ile Gly Leu Leu Cys Val Met Ala Ser Ser Ala Leu Leu Trp Met Ala
 2180 2185 2190
 Ser Val Glu Pro His Trp Ile Ala Ala Ser Ile Ile Leu Glu Phe Phe
 2195 2200 2205
 Leu Met Val Leu Leu Ile Pro Glu Pro Asp Arg Gln Arg Thr Pro Gln
 2210 2215 2220
 Asp Asn Gln Leu Ala Tyr Val Val Ile Gly Leu Leu Phe Met Ile Leu
 2225 2230 2235 2240
 Thr Val Ala Ala Asn Glu Met Gly Leu Leu Glu Thr Thr Lys Lys Asp
 2245 2250 2255
 Leu Gly Ile Gly His Val Ala Ala Glu Asn His His His Ala Thr Met
 2260 2265 2270

Leu Asp Val Asp Leu His Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val
 2275 2280 2285
 Ala Thr Thr Ile Ile Thr Pro Met Met Arg His Thr Ile Glu Asn Thr
 2290 2295 2300
 Thr Ala Asn Ile Ser Leu Thr Ala Ile Ala Asn Gln Ala Ala Ile Leu
 2305 2310 2315 2320
 Met Gly Leu Asp Lys Gly Trp Pro Ile Ser Lys Met Asp Ile Gly Val
 2325 2330 2335
 Pro Leu Leu Ala Leu Gly Cys Tyr Ser Gln Val Asn Pro Leu Thr Leu
 2340 2345 2350
 Ile Ala Ala Val Leu Met Leu Val Ala His Tyr Ala Ile Ile Gly Pro
 2355 2360 2365
 Gly Leu Gln Ala Lys Ala Thr Arg Glu Ala Gln Lys Arg Thr Ala Ala
 2370 2375 2380
 Gly Ile Met Lys Asn Pro Thr Val Asp Gly Ile Val Ala Ile Asp Leu
 2385 2390 2395 2400
 Asp Pro Val Val Tyr Asp Ala Lys Phe Glu Lys Gln Leu Gly Gln Ile
 2405 2410 2415
 Met Leu Leu Ile Leu Cys Thr Ser Gln Ile Leu Leu Met Arg Thr Thr
 2420 2425 2430
 Trp Ala Leu Cys Glu Ser Ile Thr Leu Ala Thr Gly Pro Leu Thr Thr
 2435 2440 2445
 Leu Trp Glu Gly Ser Pro Gly Lys Phe Trp Asn Thr Thr Ile Ala Val
 2450 2455 2460
 Ser Met Ala Asn Ile Phe Arg Gly Ser Tyr Leu Ala Gly Ala Gly Leu
 2465 2470 2475 2480
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 2485 2490 2495
 Ala Gln Gly Glu Thr Leu Gly Glu Lys Trp Lys Arg Gln Leu Asn Gln
 2500 2505 2510
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 2515 2520 2525
 Val Asp Arg Ser Glu Ala Lys Glu Gly Leu Lys Arg Gly Glu Thr Thr
 2530 2535 2540
 Lys His Ala Val Ser Arg Gly Thr Ala Lys Leu Arg Trp Phe Val Glu
 2545 2550 2555 2560
 Arg Asn Leu Val Lys Pro Glu Gly Lys Val Ile Asp Leu Gly Cys Gly
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 Arg Gly Gly Trp Ser Tyr Tyr Cys Ala Gly Leu Lys Lys Val Thr Glu
 2580 2585 2590
 Val Lys Gly Tyr Thr Lys Gly Gly Pro Gly His Glu Glu Pro Ile Pro
 2595 2600 2605
 Met Ala Thr Tyr Gly Trp Asn Leu Val Lys Leu His Ser Gly Lys Asp
 2610 2615 2620
 Val Phe Phe Ile Pro Pro Glu Lys Cys Asp Thr Leu Leu Cys Asp Ile
 2625 2630 2635 2640
 Gly Glu Ser Ser Pro Asn Pro Thr Ile Glu Glu Gly Arg Thr Leu Arg
 2645 2650 2655
 Val Leu Lys Met Val Glu Pro Trp Leu Arg Gly Asn Gln Phe Cys Ile
 2660 2665 2670
 Lys Ile Leu Asn Pro Tyr Met Pro Ser Val Val Glu Thr Leu Glu Gln
 2675 2680 2685
 Met Gln Arg Lys His Gly Gly Met Leu Val Arg Asn Pro Leu Ser Arg
 2690 2695 2700

Asn Ser Thr His Glu Met Tyr Trp Val Ser Cys Gly Thr Gly Asn Ile
 2705 2710 2715 2720
 Val Ser Ala Val Asn Met Thr Ser Arg Met Leu Leu Asn Arg Phe Thr
 2725 2730 2735
 Met Ala His Arg Lys Pro Thr Tyr Glu Arg Asp Val Asp Leu Gly Ala
 2740 2745 2750
 Gly Thr Arg His Val Ala Val Glu Pro Glu Val Ala Asn Leu Asp Ile
 2755 2760 2765
 Ile Gly Gln Arg Ile Glu Asn Ile Lys Asn Glu His Lys Ser Thr Trp
 2770 2775 2780
 His Tyr Asp Glu Asp Asn Pro Tyr Lys Thr Trp Ala Tyr His Gly Ser
 2785 2790 2795 2800
 Tyr Glu Val Lys Pro Ser Gly Ser Ala Ser Ser Met Val Asn Gly Val
 2805 2810 2815
 Val Arg Leu Leu Thr Lys Pro Trp Asp Val Ile Pro Met Val Thr Gln
 2820 2825 2830
 Ile Ala Met Thr Asp Thr Thr Pro Phe Gly Gln Gln Arg Val Phe Lys
 2835 2840 2845
 Glu Lys Val Asp Thr Arg Thr Pro Lys Ala Lys Arg Gly Thr Ala Gln
 2850 2855 2860
 Ile Met Glu Val Thr Ala Arg Trp Leu Trp Gly Phe Leu Ser Arg Asn
 2865 2870 2875 2880
 Lys Lys Pro Arg Ile Cys Thr Arg Glu Glu Phe Thr Arg Lys Val Arg
 2885 2890 2895
 Ser Asn Ala Ala Ile Gly Ala Val Phe Val Asp Glu Asn Gln Trp Asn
 2900 2905 2910
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 Gln Arg Pro Ala Lys Asn Gly Thr Val Met Asp Val Ile Ser Arg Arg
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 Thr Asn Met Glu Ala Gln Leu Ile Arg Gln Met Glu Ser Glu Gly Ile
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 Phe Leu Pro Ser Glu Leu Glu Thr Pro Asn Leu Ala Gly Arg Val Leu
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25

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 Ser Gly Asp Asp Cys Val Val Lys Pro Ile Asp Asp Arg Phe Ala Thr
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 Met Ile Asn Gln Arg Lys Lys
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 Thr Gly Arg Pro Ser Phe Asn Met Leu Lys Arg Ala Arg Asn Arg Val
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Ser Thr Val Ser Gln Leu Ala Lys Arg Phe Ser Lys Gly Leu Leu Ser	
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Gly Gln Gly Pro Met Lys Leu Val Met Ala Phe Ile Ala Phe Leu Arg	
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Phe Leu Ala Ile Pro Pro Thr Ala Gly Ile Leu Ala Arg Trp Gly Ser	
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75 80 85	
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Ile Ser Asn Met Leu Asn Ile Met Asn Arg Arg Lys Arg Ser Val Thr	
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Met Leu Leu Met Leu Leu Pro Thr Ala Leu Ala Phe His Leu Thr Thr	
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Ala Met Asp Leu Gly Glu Leu Cys Glu Asp Thr Met Thr Tyr Lys Cys	
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Pro Arg Ile Thr Glu Ala Glu Pro Asp Asp Val Asp Cys Trp Cys Asn	
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Ala Thr Asp Thr Trp Val Thr Tyr Gly Thr Cys Ser Gln Thr Gly Glu	
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His Arg Arg Asp Lys Arg Ser Val Ala Leu Ala Pro His Val Gly Leu	
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Gly Leu Glu Thr Arg Ala Glu Thr Trp Met Ser Ser Glu Gly Ala Trp	
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27

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gcc aac tgt tta aga aaa aac ggg aaa cgg gtg atc caa ttg agc aga Ala Asn Cys Leu Arg Lys Asn Gly Lys Arg Val Ile Gln Leu Ser Arg 1850 1855 1860	5683
aaa acc ttt gac act gag tac cag aaa aca aaa aac aac gac tgg gac Lys Thr Phe Asp Thr Glu Tyr Gln Lys Thr Lys Asn Asn Asp Trp Asp 1865 1870 1875	5731
tat gtc gtc aca aca gac att tcc gaa atg gga gca aat ttc cgg gcc Tyr Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Arg Ala 1880 1885 1890 1895	5779
gac agg gta ata gac cca agg cgg tgt ctg aaa ccg gta ata cta aaa Asp Arg Val Ile Asp Pro Arg Arg Cys Leu Lys Pro Val Ile Leu Lys 1900 1905 1910	5827
gat ggt cca gag cgc gtc att cta gcc gga ccg atg cca gtg act gtg Asp Gly Pro Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr Val 1915 1920 1925	5875
gcc agt gcc gcc cag agg aga gga aga att gga agg aac caa aac aag Ala Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Gln Asn Lys 1930 1935 1940	5923
gaa ggt gat cag tat att tac atg gga cag cct tta aac aat gat gag Glu Gly Asp Gln Tyr Ile Tyr Met Gly Gln Pro Leu Asn Asn Asp Glu 1945 1950 1955	5971

gac cac gct cat tgg aca gaa gca aag atg ctc ctt gac aat ata aac Asp His Ala His Trp Thr Glu Ala Lys Met Leu Leu Asp Asn Ile Asn 1960 1965 1970 1975	6019
aca cca gaa ggg att atc cca gcc ctc ttt gag ccg gag aga gaa aag Thr Pro Glu Gly Ile Ile Pro Ala Leu Phe Glu Pro Glu Arg Glu Lys 1980 1985 1990	6067
agt gca gct ata gac ggg gaa tac aga ctg cgg ggt gaa gca agg aaa Ser Ala Ala Ile Asp Gly Glu Tyr Arg Leu Arg Gly Glu Ala Arg Lys 1995 2000 2005	6115
acg ttc gtg gag ctc atg aga aga ggg gat cta cca gtc tgg cta tcc Thr Phe Val Glu Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ser 2010 2015 2020	6163
tac aaa gtt gcc tca gaa ggc ttc cag tac tcc gac aga agg tgg tgc Tyr Lys Val Ala Ser Glu Gly Phe Gln Tyr Ser Asp Arg Arg Trp Cys 2025 2030 2035	6211
ttc gat ggg gaa agg aac aac cag gtg ttg gag gag aac atg gac gtg Phe Asp Gly Glu Arg Asn Asn Gln Val Leu Glu Ala Asn Met Asp Val 2040 2045 2050 2055	6259
gag atc tgg aca aaa gaa gga gaa aga aag aaa cta cga cct cgc tgg Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys Lys Leu Arg Pro Arg Trp 2060 2065 2070	6307
ttg gac gcc aga aca tac tct gac cca ctg gct ctg cgc gag ttt aaa Leu Asp Ala Arg Thr Tyr Ser Asp Pro Leu Ala Leu Arg Glu Phe Lys 2075 2080 2085	6355
gag ttt gca gca gga aga aga agc gtc tca ggt gac cta ata tta gaa Glu Phe Ala Ala Gly Arg Arg Ser Val Ser Gly Asp Leu Ile Leu Glu 2090 2095 2100	6403
ata ggg aaa ctt cca caa cat ttg acg caa agg gcc cag aat gct ttg Ile Gly Lys Leu Pro Gln His Leu Thr Gln Arg Ala Gln Asn Ala Leu 2105 2110 2115	6451
gac aac ttg gtc atg ttg cac aat tcc gaa caa gga gga aaa gcc tat Asp Asn Leu Val Met Leu His Asn Ser Glu Gln Gly Gly Lys Ala Tyr 2120 2125 2130 2135	6499
aga cat gct atg gaa gaa ctg cca gac aca ata gaa acg ttg atg ctc Arg His Ala Met Glu Glu Leu Pro Asp Thr Ile Glu Thr Leu Met Leu 2140 2145 2150	6547
cta gcc ttg ata gct gtg ttg act ggt gga gtg acg ctg ttc ttc cta Leu Ala Leu Ile Ala Val Leu Thr Gly Gly Val Thr Leu Phe Phe Leu 2155 2160 2165	6595
tca gga aga ggt cta gga aaa aca tct atc ggc tta ctc tgc gtg atg Ser Gly Arg Gly Leu Gly Lys Thr Ser Ile Gly Leu Leu Cys Val Met 2170 2175 2180	6643

gcc tca agc gca ctg tta tgg atg gcc agt gtg gag ccc cat tgg ata Ala Ser Ser Ala Leu Leu Trp Met Ala Ser Val Glu Pro His Trp Ile 2185 2190 2195	6691
gcg gcc tcc atc ata ctg gag ttc ttt ctg atg gta ctg ctt att cca Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Met Val Leu Leu Ile Pro 2200 2205 2210 2215	6739
gag cca gac aga cag cgc act cca cag gac aac cag cta gca tat gtg Glu Pro Asp Arg Gln Arg Thr Pro Gln Asp Asn Gln Leu Ala Tyr Val 2220 2225 2230	6787
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gga tta ttg gaa acc aca aag aaa gac ctg ggg att ggc cat gta gct Gly Leu Leu Glu Thr Thr Lys Lys Asp Leu Gly Ile Gly His Val Ala 2250 2255 2260	6883
gct gaa aac cac cac cat gct aca atg ctg gac gta gac cta cat cca Ala Glu Asn His His His Ala Thr Met Leu Asp Val Asp Leu His Pro 2265 2270 2275	6931
gct tca gcc tgg acc ctc tat gca gtg gcc aca aca atc atc act cct Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Ile Ile Thr Pro 2280 2285 2290 2295	6979
atg atg aga cac aca att gaa aac aca acg gca aat att tcc ctg aca Met Met Arg His Thr Ile Glu Asn Thr Thr Ala Asn Ile Ser Leu Thr 2300 2305 2310	7027
gcc atc gca aac caa gca gct ata ttg atg gga ctt gac aag gga tgg Ala Ile Ala Asn Gln Ala Ala Ile Leu Met Gly Leu Asp Lys Gly Trp 2315 2320 2325	7075
cca ata tcg aag atg gac ata gga gtt cca ctt ctc gcc ttg ggg tgc Pro Ile Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala Leu Gly Cys 2330 2335 2340	7123
tat tcc caa gtg aat ccg ctg aca ctg ata gcg gca gta ttg atg cta Tyr Ser Gln Val Asn Pro Leu Thr Leu Ile Ala Ala Val Leu Met Leu 2345 2350 2355	7171
gta gct cat tac gcc ata att gga cct gga ctg caa gca aaa gct act Val Ala His Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr 2360 2365 2370 2375	7219
aga gaa gct caa aaa aga aca gcg gct gga ata atg aaa aat cca act Arg Glu Ala Gln Lys Arg Thr Ala Ala Gly Ile Met Lys Asn Pro Thr 2380 2385 2390	7267

37

gtc gac ggg att gtt gca ata gac tta gat ccc gtg gtt tac gat gca Val Asp Gly Ile Val Ala Ile Asp Leu Asp Pro Val Val Tyr Asp Ala 2395 2400 2405	7315
aaa ttt gaa aaa cag cta ggc caa ata atg ttg ttg ata ctt tgc aca Lys Phe Glu Lys Gln Leu Gly Gln Ile Met Leu Leu Ile Leu Cys Thr 2410 2415 2420	7363
tca cag att ctt ttg atg cgg act aca tgg gcc ttg tgt gaa tcc atc Ser Gln Ile Leu Leu Met Arg Thr Thr Trp Ala Leu Cys Glu Ser Ile 2425 2430 2435	7411
aca ttg gct act gga cct ctg acc act ctt tgg gag gga tct cca gga Thr Leu Ala Thr Gly Pro Leu Thr Thr Leu Trp Glu Gly Ser Pro Gly 2440 2445 2450 2455	7459
aaa ttc tgg aac acc aca ata gcg gta tcc atg gca aac att ttc agg Lys Phe Trp Asn Thr Thr Ile Ala Val Ser Met Ala Asn Ile Phe Arg 2460 2465 2470	7507
ggg agt tat cta gca gga gca ggt ctg gcc ttc tca tta atg aaa tct Gly Ser Tyr Leu Ala Gly Ala Gly Leu Ala Phe Ser Leu Met Lys Ser 2475 2480 2485	7555
cta gga gga ggt agg aga ggc acg gga gcc caa ggg gaa aca ctg gga Leu Gly Gly Gly Arg Arg Gly Thr Gly Ala Gln Gly Glu Thr Leu Gly 2490 2495 2500	7603
gaa aaa tgg aaa aga caa cta aac caa ctg agc aag tca gaa ttc aat Glu Lys Trp Lys Arg Gln Leu Asn Gln Leu Ser Lys Ser Glu Phe Asn 2505 2510 2515	7651
act tac aag agg agt ggg att atg gag gtg gat aga tcc gaa gcc aaa Thr Tyr Lys Arg Ser Gly Ile Met Glu Val Asp Arg Ser Glu Ala Lys 2520 2525 2530 2535	7699
gag gga ctg aaa aga gga gaa aca acc aaa cac gca gta tcg aga gga Glu Gly Leu Lys Arg Gly Glu Thr Thr Lys His Ala Val Ser Arg Gly 2540 2545 2550	7747
acg gcc aaa ctg agg tgg ttc gtg gag agg aac ctt gtg aaa cca gaa Thr Ala Lys Leu Arg Trp Phe Val Glu Arg Asn Leu Val Lys Pro Glu 2555 2560 2565	7795
ggg aaa gtc ata gac ctg ggt tgt gga aga ggt ggc tgg tca tat tat Gly Lys Val Ile Asp Leu Gly Cys Gly Arg Gly Gly Trp Ser Tyr Tyr 2570 2575 2580	7843
tgc gct ggg ctg aag aaa gtc aca gaa gtg aaa gga tac aca aaa gga Cys Ala Gly Leu Lys Lys Val Thr Glu Val Lys Gly Tyr Thr Lys Gly 2585 2590 2595	7891
gga cct gga cat gag gaa cca atc cca atg gcg acc tat gga tgg aac Gly Pro Gly His Glu Glu Pro Ile Pro Met Ala Thr Tyr Gly Trp Asn 2600 2605 2610 2615	7939

cta gta aag ctg cac tcc gga aaa gat gta ttt ttt ata cca cct gag	7987
Leu Val Lys Leu His Ser Gly Lys Asp Val Phe Phe Ile Pro Pro Glu	
2620 2625 2630	
aaa tgt gac acc ctt ttg tgt gat att ggt gag tcc tct ccg aac cca	8035
Lys Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro	
2635 2640 2645	
act ata gag gaa gga aga acg tta cgt gtt ctg aaa atg gtg gaa cca	8083
Thr Ile Glu Glu Gly Arg Thr Leu Arg Val Leu Lys Met Val Glu Pro	
2650 2655 2660	
tgg ctg aga gga aac caa ttt tgc ata aaa att cta aat ccc tat atg	8131
Trp Leu Arg Gly Asn Gln Phe Cys Ile Lys Ile Leu Asn Pro Tyr Met	
2665 2670 2675	
ccg agc gtg gta gaa act ctg gaa caa atg caa aga aaa cat gga gga	8179
Pro Ser Val Val Glu Thr Leu Glu Gln Met Gln Arg Lys His Gly gly	
2680 2685 2690 2695	
atg cta gtg cga aac cca ctg tca aga aat tcc acc cat gaa atg tac	8227
Met Leu Val Arg Asn Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr	
2700 2705 2710	
tgg gtt tca tgt gga aca gga aac att gtg tca gca gta aac atg aca	8275
Trp Val Ser Cys Gly Thr Gly Asn Ile Val Ser Ala Val Asn Met Thr	
2715 2720 2725	
tct aga atg ttg cta aat cgg ttc aca atg gct cac agg aag cca aca	8323
Ser Arg Met Leu Leu Asn Arg Phe Thr Met Ala His Arg Lys Pro Thr	
2730 2735 2740	
tat gaa aga gac gtg gac tta ggc gct gga aca aga cat gtg gca gta	8371
Tyr Glu Arg Asp Val Asp Leu Gly Ala Gly Thr Arg His Val Ala Val	
2745 2750 2755	
gaa cca gag gta gcc aac cta gat atc att ggc cag agg ata gag aat	8419
Glu Pro Glu Val Ala Asn Leu Asp Ile Ile Gly Gln Arg Ile Glu Asn	
2760 2765 2770 2775	
ata aaa aat gaa cat aag tca aca tgg cat tat gat gag gac aat cca	8467
Ile Lys Asn Glu His Lys Ser Thr Trp His Tyr Asp Glu Asp Asn Pro	
2780 2785 2790	
tac aaa aca tgg gcc tat cat gga tca tat gag gtt aag cca tca gga	8515
Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Val Lys Pro Ser Gly	
2795 2800 2805	
tcg gcc tca tcc atg gtc aat ggc gtg gtg aga ttg ctg acc aaa cca	8563
Ser Ala Ser Ser Met Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro	
2810 2815 2820	

39

tgg gat gtt atc ccc atg gtc aca caa ata gcc atg act gat acc aca Trp Asp Val Ile Pro Met Val Thr Gln Ile Ala Met Thr Asp Thr Thr 2825 2830 2835	8611
ccc ttt gga caa cag agg gtg ttt aaa gag aaa gtt gac acg cgc aca Pro Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr 2840 2845 2850 2855	8659
cca aaa gca aaa cgt ggc aca gca caa att atg gaa gtg aca gcc agg Pro Lys Ala Lys Arg Gly Thr Ala Gln Ile Met Glu Val Thr Ala Arg 2860 2865 2870	8707
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gac gaa cgg ttc tgg gaa ctt gtc cac aga gag agg gag ctt cat aaa Asp Glu Arg Phe Trp Glu Leu Val His Arg Glu Arg Glu Leu His Lys 2920 2925 2930 2935	8899
cag ggg aaa tgt gcc acg tgt gtc tac aat atg atg ggg aag aga gag Gln Gly Lys Cys Ala Thr Cys Val Tyr Asn Met Met Gly Lys Arg Glu 2940 2945 2950	8947
aaa aaa tta gga gag ttc gga aag gca aaa gga agt cgt gca ata tgg Lys Lys Leu Gly Glu Phe Gly Lys Ala Lys Gly Ser Arg Ala Ile Trp 2955 2960 2965	8995
tac atg tgg ttg gga gca cgc ttc cta gag ttt gaa gcc ctt ggt ttc Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu Phe Glu Ala Leu Gly Phe 2970 2975 2980	9043
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gaa gga gaa gga ctc cac aaa ctt gga tac ata ctc aga gac ata tca Glu Gly Glu Gly Leu His Lys Leu Gly Tyr Ile Leu Arg Asp Ile Ser 3000 3005 3010 3015	9139
agg att cca ggg ggg aac atg tat gca gat gac aca gcc gga tgg gac Arg Ile Pro Gly Gly Asn Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp 3020 3025 3030	9187
aca aga ata aca gag gat gat ctc cag aat gag gct aaa atc act gac Thr Arg Ile Thr Glu Asp Asp Leu Gln Asn Glu Ala Lys Ile Thr Asp 3035 3040 3045	9235

atc atg gag ccc gaa cat gcc ctg ctg gct acg tca atc ttt aag ctg Ile Met Glu Pro Glu His Ala Leu Leu Ala Thr Ser Ile Phe Lys Leu 3050 3055 3060	9283
acc tac caa aat aag gtg gta agg gtg cag aga cca gca aaa aat gga Thr Tyr Gln Asn Lys Val Val Arg Val Gln Arg Pro Ala Lys Asn Gly 3065 3070 3075	9331
acc gtg atg gat gtt ata tcc aga cgt gac cag aga ggc agt gga cag Thr Val Met Asp Val Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly Gln 3080 3085 3090 3095	9379
gtt gga act tat ggc tta aac act ttc acc aac atg gag gcc caa ctg Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu 3100 3105 3110	9427
ata aga caa atg gag tct gag gga atc ttt tta ccc agc gaa ttg gaa Ile Arg Gln Met Glu Ser Glu Gly Ile Phe Leu Pro Ser Glu Leu Glu 3115 3120 3125	9475
acc cca aat cta gcc gga aga gtt ctc gac tgg ttg gaa aaa tat ggt Thr Pro Asn Leu Ala Gly Arg Val Leu Asp Trp Leu Glu Lys Tyr Gly 3130 3135 3140	9523
gtc gaa agg ctg aaa aga atg gca atc agc gga gat gac tgt gtg gtg Val Glu Arg Leu Lys Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val 3145 3150 3155	9571
aaa cca att gat gac agg ttc gca aca gcc tta aca gct ttg aat gac Lys Pro Ile Asp Asp Arg Phe Ala Thr Ala Leu Thr Ala Leu Asn Asp 3160 3165 3170 3175	9619
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cta att atg aag gat ggg agg gag ata gtg gtg cca tgc cgc aac caa Leu Ile Met Lys Asp Gly Arg Glu Ile Val Val Pro Cys Arg Asn Gln 3210 3215 3220	9763
gat gaa ctt gtg ggg agg gcc aga gta tca caa ggc gcc gga tgg agc Asp Glu Leu Val Gly Arg Ala Arg Val Ser Gln Gly Ala Gly Trp Ser 3225 3230 3235	9811
ctg aga gaa acc gca tgc cta ggc aag tca tat gca caa atg tgg cag Leu Arg Glu Thr Ala Cys Leu Gly Lys Ser Tyr Ala Gln Met Trp Gln 3240 3245 3250 3255	9859

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ctg atg tat ttc cac agg aga gac ctg aga ctg gcg gct aac gct att      9907
Leu Met Tyr Phe His Arg Arg Asp Leu Arg Leu Ala Ala Asn Ala Ile
                3260                3265                3270

tgt tca gcc gtt cca gtt gat tgg gtc cca acc agc cgc acc acc tgg      9955
Cys Ser Ala Val Pro Val Asp Trp Val Pro Thr Ser Arg Thr Thr Trp
                3275                3280                3285

tcg atc cat gcc cat cac caa tgg atg aca aca gaa gac atg tta tca      10003
Ser Ile His Ala His His Gln Trp Met Thr Thr Glu Asp Met Leu Ser
                3290                3295                3300

gta tgg aat agg gtc tgg ata gag gaa aac cca tgg atg gag gat aag      10051
Val Trp Asn Arg Val Trp Ile Glu Glu Asn Pro Trp Met Glu Asp Lys
                3305                3310                3315

act cat gtg tcc agt tgg gaa gaa gtt cca tac cta gga aag agg gaa      10099
Thr His Val Ser Ser Trp Glu Glu Val Pro Tyr Leu Gly Lys Arg Glu
                3320                3325                3330                3335

gat cag tgg tgt gga tcc ctg ata ggc tta aca gca agg gcc acc tgg      10147
Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ala Arg Ala Thr Trp
                3340                3345                3350

gcc act aat ata caa gtg gcc ata aac caa gtg aga agg ctc att ggg      10195
Ala Thr Asn Ile Gln Val Ala Ile Asn Gln Val Arg Arg Leu Ile Gly
                3355                3360                3365

aat gag aat tat cta gat tac atg aca tca atg aag aga ttc aag aat      10243
Asn Glu Asn Tyr Leu Asp Tyr Met Thr Ser Met Lys Arg Phe Lys Asn
                3370                3375                3380

gag agt gat ccc gaa ggg gca ctc tgg taa gtcaacacat tcacaaaata      10293
Glu Ser Asp Pro Glu Gly Ala Leu Trp *
                3385                3390

aagaaaata aaaaatcaaa tgaggcaaga agtcaggcca gattaagcca tagtacggta 10353
agagctatgc tgcctgtgag ccccgctccaa ggacgtaaaa tgaagtcagg cggaaagcca 10413
cggtttgagc aagccgtgtct cctctgtggct ccacgtgggg gatgtaaaaa ccggggaggc 10473
tgcaacccat ggaagctgta cgcctgtgggt agcagactag tggttagagg agaccctcc 10533
caagacacaa cgcagcagcg gggcccaaca ccagggggaag ctgtaccctg gtggtaagga 10593
ctagagggtta gaggagacc ccgcgctaac aataaacagc atattgacgc tgggagagac 10653
cagagatcct gctgtctcta cagcatcatt ccaggcacag aagccacgaa aatggaatgg 10713
tgtgttgaa tcaacagggt ct                                     10735

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<210> 4

<211> 3392

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<400> 4

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Met Ile Asn Gln Arg Lys Lys Thr Gly Arg Pro Ser Phe Asn Met Leu
 1          5          10          15
Lys Arg Ala Arg Asn Arg Val Ser Thr Val Ser Gln Leu Ala Lys Arg
      20          25          30
Phe Ser Lys Gly Leu Leu Ser Gly Gln Gly Pro Met Lys Leu Val Met
      35          40          45
Ala Phe Ile Ala Phe Leu Arg Phe Leu Ala Ile Pro Pro Thr Ala Gly
      50          55          60
Ile Leu Ala Arg Trp Gly Ser Phe Lys Lys Asn Gly Ala Ile Lys Val
65          70          75          80
Leu Arg Gly Phe Lys Arg Glu Ile Ser Asn Met Leu Asn Ile Met Asn
      85          90          95
Arg Arg Lys Arg Ser Val Thr Met Leu Leu Met Leu Leu Pro Thr Ala
      100          105          110
Leu Ala Phe His Leu Thr Thr Arg Gly Gly Glu Pro His Met Ile Val
      115          120          125
Ser Lys Gln Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ser Ala Gly
      130          135          140
Val Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Leu Cys Glu
      145          150          155          160
Asp Thr Met Thr Tyr Lys Cys Pro Arg Ile Thr Glu Ala Glu Pro Asp
      165          170          175
Asp Val Asp Cys Trp Cys Asn Ala Thr Asp Thr Trp Val Thr Tyr Gly
      180          185          190
Thr Cys Ser Gln Thr Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala
      195          200          205
Leu Ala Pro His Val Gly Leu Gly Leu Glu Thr Arg Ala Glu Thr Trp
      210          215          220
Met Ser Ser Glu Gly Ala Trp Lys Gln Ile Gln Lys Val Glu Thr Trp
      225          230          235          240
Ala Leu Arg His Pro Gly Phe Thr Val Ile Ala Leu Phe Leu Ala His
      245          250          255
Ala Ile Gly Thr Ser Ile Thr Gln Lys Gly Ile Ile Phe Ile Leu Leu
      260          265          270
Met Leu Val Thr Pro Ser Met Ala Met Arg Cys Val Gly Ile Gly Asn
      275          280          285
Arg Asp Phe Val Glu Gly Leu Ser Gly Ala Thr Trp Val Asp Val Val
      290          295          300
Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr
      305          310          315          320
Leu Asp Ile Glu Leu Leu Lys Thr Glu Val Thr Asn Pro Ala Val Leu
      325          330          335
Arg Lys Leu Cys Ile Glu Ala Lys Ile Ser Asn Thr Thr Thr Asp Ser
      340          345          350
Arg Cys Pro Thr Gln Gly Glu Ala Thr Leu Val Glu Glu Gln Asp Ala
      355          360          365
Asn Phe Val Cys Arg Arg Thr Phe Val Asp Arg Gly Trp Gly Asn Gly
      370          375          380
Cys Gly Leu Phe Gly Lys Gly Ser Leu Ile Thr Cys Ala Lys Phe Lys
      385          390          395          400
Cys Val Thr Lys Leu Glu Gly Lys Ile Ala Gln Tyr Glu Asn Leu Lys
      405          410          415
Tyr Ser Val Ile Val Thr Val His Thr Gly Asp Gln His Gln Val Gly
      420          425          430

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Asn Glu Thr Thr Glu His Gly Thr Thr Ala Thr Ile Thr Pro Gln Ala
 435 440 445
 Pro Thr Ser Glu Ile Gln Leu Thr Asp Tyr Gly Thr Leu Thr Leu Asp
 450 455 460
 Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Thr
 465 470 475 480
 Met Lys Lys Lys Ser Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu
 485 490 495
 Pro Leu Pro Trp Thr Ser Gly Ala Leu Thr Ser Gln Glu Thr Trp Asn
 500 505 510
 Arg Gln Asp Leu Leu Val Thr Phe Lys Thr Ala His Ala Lys Lys Gln
 515 520 525
 Glu Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu
 530 535 540
 Thr Gly Ala Thr Glu Ile Gln Thr Ser Gly Thr Thr Thr Ile Phe Ala
 545 550 555 560
 Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Thr Leu Lys Gly
 565 570 575
 Met Ser Tyr Val Met Cys Thr Gly Ser Phe Lys Leu Glu Lys Glu Val
 580 585 590
 Ala Glu Thr Gln His Gly Thr Val Leu Val Gln Val Lys Tyr Glu Gly
 595 600 605
 Thr Asp Ala Pro Cys Lys Ile Pro Phe Ser Thr Gln Asp Glu Lys Gly
 610 615 620
 Ala Thr Gln Asn Gly Arg Leu Ile Thr Ala Asn Pro Ile Val Thr Asp
 625 630 635 640
 Lys Glu Lys Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Glu Ser
 645 650 655
 Tyr Ile Val Val Gly Ala Gly Glu Lys Ala Leu Lys Leu Ser Trp Phe
 660 665 670
 Lys Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly
 675 680 685
 Ala Arg Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser
 690 695 700
 Ile Gly Gly Val Phe Thr Ser Met Gly Lys Leu Val His Gln Val Phe
 705 710 715 720
 Gly Thr Ala Tyr Gly Val Leu Phe Ser Gly Val Ser Trp Thr Met Lys
 725 730 735
 Ile Gly Ile Gly Ile Leu Leu Thr Trp Leu Gly Leu Asn Ser Arg Asn
 740 745 750
 Thr Ser Leu Ser Val Met Cys Ile Ala Val Gly Met Val Thr Leu Tyr
 755 760 765
 Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Ile Asn Trp Lys
 770 775 780
 Gly Arg Glu Leu Lys Cys Gly Ser Gly Ile Phe Val Thr Asn Glu Val
 785 790 795
 His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Ala Asp Ser Pro Lys Arg
 805 810 815
 Leu Ser Ala Ala Ile Gly Lys Ala Trp Glu Glu Gly Val Cys Gly Ile
 820 825 830
 Arg Ser Ala Thr Arg Leu Glu Asn Ile Met Trp Lys Gln Ile Ser Asn
 835 840 845
 Glu Leu Asn His Ile Leu Leu Glu Asn Asp Met Lys Phe Thr Val Val
 850 855 860

Val Gly Asp Val Ser Gly Ile Leu Ala Gln Gly Lys Lys Met Ile Arg
 865 870 875 880
 Pro Gln Pro Met Glu His Lys Tyr Ser Trp Lys Ser Trp Gly Lys Ala
 885 890 895
 Lys Ile Ile Gly Ala Asp Val Gln Asn Thr Thr Phe Ile Ile Asp Gly
 900 905 910
 Pro Asn Thr Pro Glu Cys Pro Asp Asn Gln Arg Ala Trp Asn Ile Trp
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 synthetic construct

<221> CDS

<222> (97)...(10272)

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                               1                               5

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Lys Thr Gly Arg Pro Ser Phe Asn Met Leu Lys Arg Ala Arg Asn Arg
                               10                               15                               20

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Ser Gly Gln Gly Pro Met Lys Leu Val Met Ala Phe Ile Ala Phe Leu
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Thr Met Leu Leu Met Leu Leu Pro Thr Ala Leu Ala Phe His Leu Thr
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51

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ttg ttt agc gga gtt tct tgg acc atg aaa ata gga ata ggg att ctg Leu Phe Ser Gly Val Ser Trp Thr Met Lys Ile Gly Ile Gly Ile Leu 730 735 740	2322
ctg aca tgg cta gga tta aat tca agg aac acg tcc ctt tgc gtg atg Leu Thr Trp Leu Gly Leu Asn Ser Arg Asn Thr Ser Leu Ser Val Met 745 750 755	2370
tgc atc gca gcc ggc att gtg aca ctg tat ttg gga gtc atg gtg cag Cys Ile Ala Ala Gly Ile Val Thr Leu Tyr Leu Gly Val Met Val Gln 760 765 770	2418
gcc gat agt ggt tgc gtt gtg agc tgg aaa aac aaa gaa ctg aaa tgt Ala Asp Ser Gly Cys Val Val Ser Trp Lys Asn Lys Glu Leu Lys Cys 775 780 785 790	2466
ggc agt ggg att ttc atc aca gac aac gtg cac aca tgg aca gaa caa Gly Ser Gly Ile Phe Ile Thr Asp Asn Val His Thr Trp Thr Glu Gln 795 800 805	2514
tac aag ttc caa cca gaa tcc cct tca aaa cta gct tca gct atc cag Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys Leu Ala Ser Ala Ile Gln 810 815 820	2562
aaa gcc cat gaa gag gac att tgt gga atc cgc tca gta aca aga ctg Lys Ala His Glu Glu Asp Ile Cys Gly Ile Arg Ser Val Thr Arg Leu 825 830 835	2610

gag aat ctg atg tgg aaa caa ata aca cca gaa ttg aat cac att cta Glu Asn Leu Met Trp Lys Gln Ile Thr Pro Glu Leu Asn His Ile Leu 840 845 850	2658
tca gaa aat gag gtg aag tta act att atg aca gga gac atc aaa gga Ser Glu Asn Glu Val Lys Leu Thr Ile Met Thr Gly Asp Ile Lys Gly 855 860 865 870	2706
atc atg cag gca gga aaa cga tct ctg cgg cct cag ccc act gag ctg Ile Met Gln Ala Gly Lys Arg Ser Leu Arg Pro Gln Pro Thr Glu Leu 875 880 885	2754
aag tat tca tgg aaa aca tgg ggc aaa gca aaa atg ctc tct aca gag Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala Lys Met Leu Ser Thr Glu 890 895 900	2802
tct cat aac cag acc ttt ctc att gat ggc ccc gaa aca gca gaa tgc Ser His Asn Gln Thr Phe Leu Ile Asp Gly Pro Glu Thr Ala Glu Cys 905 910 915	2850
ccc aac aca aat aga gct tgg aat tcg ttg gaa gtt gaa gac tat ggc Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu Glu Val Glu Asp Tyr Gly 920 925 930	2898
ttt gga gta ttc acc acc aat ata tgg cta aaa ttg aaa gaa aaa cag Phe Gly Val Phe Thr Thr Asn Ile Trp Leu Lys Leu Lys Glu Lys Gln 935 940 945 950	2946
gat gta ttc tgc gac tca aaa ctc atg tca gcg gcc ata aaa gac aac Asp Val Phe Cys Asp Ser Lys Leu Met Ser Ala Ala Ile Lys Asp Asn 955 960 965	2994
aga gcc gtc cat gcc gat atg ggt tat tgg ata gaa agt gca ctc aat Arg Ala Val His Ala Asp Met Gly Tyr Trp Ile Glu Ser Ala Leu Asn 970 975 980	3042
gac aca tgg aag ata gag aaa gcc tct ttc att gaa gtt aaa aac tgc Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe Ile Glu Val Lys Asn Cys 985 990 995	3090
cac tgg cca aaa tca cac acc ctc tgg agc aat gga gtg cta gaa agt His Trp Pro Lys Ser His Thr Leu Trp Ser Asn Gly Val Leu Glu Ser 1000 1005 1010	3138
gag atg ata att cca aag aat ctc gct gga cca gtg tct caa cac aac Glu Met Ile Ile Pro Lys Asn Leu Ala Gly Pro Val Ser Gln His Asn 1015 1020 1025 1030	3186
tat aga cca ggc tac cat aca caa ata aca gga cca tgg cat cta ggt Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr Gly Pro Trp His Leu Gly 1035 1040 1045	3234

55

aag ctt gag atg gac ttt gat ttc tgt gat gga aca aca gtg gta gtg Lys Leu Glu Met Asp Phe Asp Phe Cys Asp Gly Thr Thr Val Val Val	3282
1050 1055 1060	
act gag gac tgc gga aat aga gga ccc tct ttg aga aca acc act gcc Thr Glu Asp Cys Gly Asn Arg Gly Pro Ser Leu Arg Thr Thr Thr Ala	3330
1065 1070 1075	
tct gga aaa ctc ata aca gaa tgg tgc tgc cga tct tgc aca tta cca Ser Gly Lys Leu Ile Thr Glu Trp Cys Cys Arg Ser Cys Thr Leu Pro	3378
1080 1085 1090	
cag cta aga tac aga ggt gag gat ggg tgc tgg tac ggg atg gaa atc Pro Leu Arg Tyr Arg Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile	3426
1095 1100 1105 1110	
aga cca ttg aag gag aaa gaa gag aat ttg gtc aac tcc ttg gtc aca Arg Pro Leu Lys Glu Lys Glu Glu Asn Leu Val Asn Ser Leu Val Thr	3474
1115 1120 1125	
gct gga cat ggg cag gtc gac aac ttt tca cta gga gtc ttg gga atg Ala Gly His Gly Gln Val Asp Asn Phe Ser Leu Gly Val Leu Gly Met	3522
1130 1135 1140	
gca ttg ttc ctg gag gaa atg ctt agg acc cga gta gga acg aaa cat Ala Leu Phe Leu Glu Glu Met Leu Arg Thr Arg Val Gly Thr Lys His	3570
1145 1150 1155	
gca ata cta cta gtt gca gtt tct ttt gtg aca ttg atc aca ggg aac Ala Ile Leu Leu Val Ala Val Ser Phe Val Thr Leu Ile Thr Gly Asn	3618
1160 1165 1170	
atg tcc ttt aga gac ctg gga aga gtg atg gtt atg gta ggc gcc act Met Ser Phe Arg Asp Leu Gly Arg Val Met Val Met Val Gly Ala Thr	3666
1175 1180 1185 1190	
atg acg gat gac ata ggt atg ggc gtg act tat ctt gcc cta cta gca Met Thr Asp Asp Ile Gly Met Gly Val Thr Tyr Leu Ala Leu Leu Ala	3714
1195 1200 1205	
gcc ttc aaa gtc aga cca act ttt gca gct gga cta ctc ttg aga aag Ala Phe Lys Val Arg Pro Thr Phe Ala Ala Gly Leu Leu Leu Arg Lys	3762
1210 1215 1220	
ctg acc tcc aag gaa ttg atg atg act act ata gga att gta ctc ctc Leu Thr Ser Lys Glu Leu Met Met Thr Thr Ile Gly Ile Val Leu Leu	3810
1225 1230 1235	
tcc cag agc acc ata cca gag acc att ctt gag ttg act gat gcg tta Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu Glu Leu Thr Asp Ala Leu	3858
1240 1245 1250	
gcc tta ggc atg atg gtc ctc aaa atg gtg aga aat atg gaa aag tat Ala Leu Gly Met Met Val Leu Lys Met Val Arg Asn Met Glu Lys Tyr	3906
1255 1260 1265 1270	

56

caa ttg gca gtg act atc atg gct atc ttg tgc gtc cca aac gca gtg Gln Leu Ala Val Thr Ile Met Ala Ile Leu Cys Val Pro Asn Ala Val 1275 1280 1285	3954
ata tta caa aac gca tgg aaa gtg agt tgc aca ata ttg gca gtg gtg Ile Leu Gln Asn Ala Trp Lys Val Ser Cys Thr Ile Leu Ala Val Val 1290 1295 1300	4002
tcc gtt tcc cca ctg ttc tta aca tcc tca cag caa aaa aca gat tgg Ser Val Ser Pro Leu Phe Leu Thr Ser Ser Gln Gln Lys Thr Asp Trp 1305 1310 1315	4050
ata cca tta gca ttg acg atc aaa ggt ctc aat cca aca gct att ttt Ile Pro Leu Ala Leu Thr Ile Lys Gly Leu Asn Pro Thr Ala Ile Phe 1320 1325 1330	4098
cta aca acc ctc tca aga acc agc aag aaa agg agc tgg cca tta aat Leu Thr Thr Leu Ser Arg Thr Ser Lys Lys Arg Ser Trp Pro Leu Asn 1335 1340 1345 1350	4146
gag gct atc atg gca gtc ggg atg gtg agc att tta gcc agt tct ctc Glu Ala Ile Met Ala Val Gly Met Val Ser Ile Leu Ala Ser Ser Leu 1355 1360 1365	4194
cta aaa aat gat att ccc atg aca gga cca tta gtg gct gga ggg ctc Leu Lys Asn Asp Ile Pro Met Thr Gly Pro Leu Val Ala Gly Gly Leu 1370 1375 1380	4242
ctc act gtg tgc tac gtg ctc act gga cga tcg gcc gat ttg gaa ctg Leu Thr Val Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu Leu 1385 1390 1395	4290
gag aga gca gcc gat gtc aaa tgg gaa gac cag gca gag ata tca gga Glu Arg Ala Ala Asp Val Lys Trp Glu Asp Gln Ala Glu Ile Ser Gly 1400 1405 1410	4338
agc agt cca atc ctg tca ata aca ata tca gaa gat ggt agc atg tcg Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser Glu Asp Gly Ser Met Ser 1415 1420 1425 1430	4386
ata aaa aat gaa gag gaa gaa caa aca ctg acc ata ctc att aga aca Ile Lys Asn Glu Glu Glu Glu Gln Thr Leu Thr Ile Leu Ile Arg Thr 1435 1440 1445	4434
gga ttg ctg gtg atc tca gga ctt ttt cot gta tca ata cca atc acg Gly Leu Leu Val Ile Ser Gly Leu Phe Pro Val Ser Ile Pro Ile Thr 1450 1455 1460	4482
gca gca gca tgg tac ctg tgg gaa gtg aag aaa caa cgg gcc gga gta Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys Lys Gln Arg Ala Gly Val 1465 1470 1475	4530

57

ttg tgg gat gtt cct tca ccc cca ccc atg gga aag gct gaa ctg gaa Leu Trp Asp Val Pro Ser Pro Pro Pro Met Gly Lys Ala Glu Leu Glu 1480 1485 1490	4578
gat gga gcc tat aga att aag caa aaa ggg att ctt gga tat tcc cag Asp Gly Ala Tyr Arg Ile Lys Gln Lys Gly Ile Leu Gly Tyr Ser Ser Gln 1495 1500 1505 1510	4626
atc gga gcc gga gtt tac aaa gaa gga aca ttc cat aca atg tgg cat Ile Gly Ala Gly Val Tyr Lys Glu Gly Thr Phe His Thr Met Trp His 1515 1520 1525	4674
gtc aca cgt ggc gct gtt cta atg cat aaa gga aag agg att gaa cca Val Thr Arg Gly Ala Val Leu Met His Lys Gly Lys Arg Ile Glu Pro 1530 1535 1540	4722
tca tgg gcg gac gtc aag aaa gac cta ata tca tat gga gga gcc tgg Ser Trp Ala Asp Val Lys Lys Asp Leu Ile Ser Tyr Gly Gly Gly Trp 1545 1550 1555	4770
aag tta gaa gga gaa tgg aag gaa gga gaa gaa gtc cag gta ttg gca Lys Leu Glu Gly Glu Trp Lys Glu Gly Glu Glu Val Gln Val Leu Ala 1560 1565 1570	4818
ctg gag cct gga aaa aat cca aga gcc gtc caa acg aaa cct ggt ctt Leu Glu Pro Gly Lys Asn Pro Arg Ala Val Gln Thr Lys Pro Gly Leu 1575 1580 1585 1590	4866
ttc aaa acc aac gcc gga aca ata ggt gct gta tct ctg gac ttt tct Phe Lys Thr Asn Ala Gly Thr Ile Gly Ala Val Ser Leu Asp Phe Ser 1595 1600 1605	4914
cct gga acg tca gga tct cca att atc gac aaa aaa gga aaa gtt gtg Pro Gly Thr Ser Gly Ser Pro Ile Ile Asp Lys Lys Gly Lys Val Val 1610 1615 1620	4962
ggc ctt tat ggt aat ggt gtt gtt aca agg agt gga gca tat gtg agt Gly Leu Tyr Gly Asn Gly Val Val Thr Arg Ser Gly Ala Tyr Val Ser 1625 1630 1635	5010
gct ata gcc cag act gaa aaa agc att gaa gac aac cca gag atc gaa Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile Glu 1640 1645 1650	5058
gat gac att ttc cga aag aga aga ctg acc atc atg gac ctc cac cca Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu His Pro 1655 1660 1665 1670	5106
gga gcg gga aag acg aag aga tac ctt ccg gcc ata gtc aga gaa gct Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro Ala Ile Val Arg Glu Ala 1675 1680 1685	5154
ata aaa cgg ggt ttg aga aca tta atc ttg gcc ccc act aga gtt gtg Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro Thr Arg Val Val 1690 1695 1700	5202

gca gct gaa atg gag gaa gcc ctt aga gga ctt cca ata aga tac cag Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu Pro Ile Arg Tyr Gln 1705 1710 1715	5250
acc cca gcc atc aga gct gtg cac acc ggg cgg gag att gtg gac cta Thr Pro Ala Ile Arg Ala Val His Thr Gly Arg Glu Ile Val Asp Leu 1720 1725 1730	5298
atg tgt cat gcc aca ttt acc atg agg ctg cta tca cca gtt aga gtg Met Cys His Ala Thr Phe Thr Met Arg Leu Leu Ser Pro Val Arg Val 1735 1740 1745 1750	5346
cca aac tac aac ctg att atc atg gac gaa gcc cat ttc aca gac cca Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu Ala His Phe Thr Asp Pro 1755 1760 1765	5394
gca agt ata gca gct aga gga tac atc tca act cga gtg gag atg ggt Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Glu Met Gly 1770 1775 1780	5442
gag gca gct ggg att ttt atg aca gcc act ccc ccg gga agc aga gac Glu Ala Ala Gly Ile Phe Met Thr Ala Thr Pro Pro Gly Ser Arg Asp 1785 1790 1795	5490
cca ttt cct cag agc aat gca cca atc ata gat gaa gaa aga gaa atc Pro Phe Pro Gln Ser Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu Ile 1800 1805 1810	5538
cct gaa cgc tcg tgg aat tcc gga cat gaa tgg gtc acg gat ttt aaa Pro Glu Arg Ser Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe Lys 1815 1820 1825 1830	5586
ggg aag act gtt tgg ttc gtt cca agt ata aaa gca gga aat gat ata Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile 1835 1840 1845	5634
gca gct tgc ctg agg aaa aat gga aag aaa gtg ata caa ctc agt agg Ala Ala Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg 1850 1855 1860	5682
aag acc ttt gat tct gag tat gtc aag act aga acc aat gat tgg gac Lys Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp 1865 1870 1875	5730
ttc gtg gtt aca act gac att tca gaa atg ggt gcc aat ttc aag gct Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys Ala 1880 1885 1890	5778
gag agg gtt ata gac ccc aga cgc tgc atg aaa cca gtc ata cta aca Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile Leu Thr 1895 1900 1905 1910	5826

59

gat ggt gaa gag cgg gtg att ctg gca gga cct atg cca gtg acc cac Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr His 1915 1920 1925	5874
tct agt gca gca caa aga aga ggg aga ata gga aga aat cca aaa aat Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro Lys Asn 1930 1935 1940	5922
gag aat gac cag tac ata tac atg ggg gaa cct ctg gaa aat gat gaa Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro Leu Glu Asn Asp Glu 1945 1950 1955	5970
gac tgt gca cac tgg aaa gaa gct aaa atg ctc cta gat aac atc aac Asp Cys Ala His Trp Lys Glu Ala Lys Met Leu Leu Asp Asn Ile Asn 1960 1965 1970	6018
acg cca gaa gga atc att cct agc atg ttc gaa cca gag cgt gaa aag Thr Pro Glu Gly Ile Ile Pro Ser Met Phe Glu Pro Glu Arg Glu Lys 1975 1980 1985 1990	6066
gtg gat gcc att gat ggc gaa tac cgc ttg aga gga gaa gca agg aaa Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu Arg Gly Glu Ala Arg Lys 1995 2000 2005	6114
acc ttt gta gac tta atg aga aga gga gac cta cca gtc tgg ttg gcc Thr Phe Val Asp Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ala 2010 2015 2020	6162
tac aga gtg gca gct gaa ggc atc aac tac gca gac aga agg tgg tgt Tyr Arg Val Ala Ala Glu Gly Ile Asn Tyr Ala Asp Arg Arg Trp Cys 2025 2030 2035	6210
ttt gat gga gtc aag aac aac caa atc cta gaa gaa aac gtg gaa gtt Phe Asp Gly Val Lys Asn Asn Gln Ile Leu Glu Glu Asn Val Glu Val 2040 2045 2050	6258
gaa atc tgg aca aaa gaa ggg gaa agg aag aaa ttg aaa ccc aga tgg Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp 2055 2060 2065 2070	6306
ttg gat gct agg atc tat tct gac cca ctg gcg cta aaa gaa ttt aag Leu Asp Ala Arg Ile Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys 2075 2080 2085	6354
gaa ttt gca gcc gga aga aag tct ctg acc ctg aac cta atc aca gaa Glu Phe Ala Ala Gly Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu 2090 2095 2100	6402
atg ggt agg ctc cca acc ttc atg act cag aag gca aga gac gca ctg Met Gly Arg Leu Pro Thr Phe Met Thr Gln Lys Ala Arg Asp Ala Leu 2105 2110 2115	6450
gac aac tta gca gtg ctg cac acg gct gag gca ggt gga agg gcg tac Asp Asn Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala Tyr 2120 2125 2130	6498

aac cat gct ctc agt gaa ctg ccg gag acc ctg gag aca ttg ctt tta Asn His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu Leu Leu 2135 2140 2145 2150	6546
ctg aca ctt ctg gct aca gtc acg gga ggg atc ttt tta ttc ttg atg Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu Phe Leu Met 2155 2160 2165	6594
agc gca agg ggc ata ggg aag atg acc ctg gga atg tgc tgc ata atc Ser Ala Arg Gly Ile Gly Lys Met Thr Leu Gly Met Cys Cys Ile Ile 2170 2175 2180	6642
acg gct agc atc ctc cta tgg tac gca caa ata cag cca cac tgg ata Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln Ile Gln Pro His Trp Ile 2185 2190 2195	6690
gca gct tca ata ata ctg gag ttt ttt ctc ata gtt ttg ctt att cca Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Ile Val Leu Leu Ile Pro 2200 2205 2210	6738
gaa cct gaa aaa cag aga aca ccc caa gac aac caa ctg acc tac gtt Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn Gln Leu Thr Tyr Val 2215 2220 2225 2230	6786
gtc ata gcc atc ctc aca gtg gtg gcc gca acc atg gca aac gag atg Val Ile Ala Ile Leu Thr Val Val Ala Ala Thr Met Ala Asn Glu Met 2235 2240 2245	6834
ggt ttc cta gaa aaa acg aag aaa gat ctc gga ttg gga agc att gca Gly Phe Leu Glu Lys Thr Lys Lys Asp Leu Gly Leu Gly Ser Ile Ala 2250 2255 2260	6882
acc cag caa ccc gag agc aac atc ctg gac ata gat cta cgt cct gca Thr Gln Gln Pro Glu Ser Asn Ile Leu Asp Ile Asp Leu Arg Pro Ala 2265 2270 2275	6930
tca gca tgg acg ctg tat gcc gtg gcc aca aca ttt gtt aca cca atg Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Phe Val Thr Pro Met 2280 2285 2290	6978
ttg aga cat agc att gaa aat tcc tca gtg aat gtg tcc cta aca gct Leu Arg His Ser Ile Glu Asn Ser Ser Val Asn Val Ser Leu Thr Ala 2295 2300 2305 2310	7026
ata gcc aac caa gcc aca gtg tta atg ggt ctc ggg aaa gga tgg cca Ile Ala Asn Gln Ala Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro 2315 2320 2325	7074
ttg tca aag atg gac atc gga gtt ccc ctt ctc gcc att gga tgc tac Leu Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala Ile Gly Cys Tyr 2330 2335 2340	7122

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tca caa gtc aac ccc ata act ctc aca gca gct ctt ttc tta ttg gta Ser Gln Val Asn Pro Ile Thr Leu Thr Ala Ala Leu Phe Leu Leu Val 2345 2350 2355	7170
gca cat tat gcc atc ata ggg cca gga ctc caa gca aaa gca acc aga Ala His Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg 2360 2365 2370	7218
gaa gct cag aaa aga gca gcg gcg ggc atc atg aaa aac cca act gtc Glu Ala Gln Lys Arg Ala Ala Ala Gly Ile Met Lys Asn Pro Thr Val 2375 2380 2385 2390	7266
gat gga ata aca gtg att gac cta gat cca ata cct tat gat cca aag Asp Gly Ile Thr Val Ile Asp Leu Asp Pro Ile Pro Tyr Asp Pro Lys 2395 2400 2405	7314
ttt gaa aag cag ttg gga caa gta atg ctc cta gtc ctc tgc gtg act Phe Glu Lys Gln Leu Gly Gln Val Met Leu Leu Val Leu Cys Val Thr 2410 2415 2420	7362
caa gta ttg atg atg agg act aca tgg gct ctg tgt gag gct tta acc Gln Val Leu Met Met Arg Thr Thr Trp Ala Leu Cys Glu Ala Leu Thr 2425 2430 2435	7410
tta gct acc ggg ccc atc tcc aca ttg tgg gaa gga aat cca ggg agg Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp Glu Gly Asn Pro Gly Arg 2440 2445 2450	7458
ttt tgg aac act acc att gcg gtg tca atg gct aac att ttt aga ggg Phe Trp Asn Thr Thr Ile Ala Val Ser Met Ala Asn Ile Phe Arg Gly 2455 2460 2465 2470	7506
agt tac ttg gcc gga gct gga ctt ctc ttt tct att atg aag aac aca Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe Ser Ile Met Lys Asn Thr 2475 2480 2485	7554
acc aac aca aga agg gga act ggc aac ata gga gag acg ctt gga gag Thr Asn Thr Arg Arg Gly Thr Gly Asn Ile Gly Glu Thr Leu Gly Glu 2490 2495 2500	7602
aaa tgg aaa agc cga ttg aac gca ttg gga aaa agt gaa ttc cag atc Lys Trp Lys Ser Arg Leu Asn Ala Leu Gly Lys Ser Glu Phe Gln Ile 2505 2510 2515	7650
tac aag aaa agt gga atc cag gaa gtg gat aga acc tta gca aaa gaa Tyr Lys Lys Ser Gly Ile Gln Glu Val Asp Arg Thr Leu Ala Lys Glu 2520 2525 2530	7698
ggc att aaa aga gga gaa acg gac cat cac gct gtg tcg cga ggc tca Gly Ile Lys Arg Gly Glu Thr Asp His His Ala Val Ser Arg Gly Ser 2535 2540 2545 2550	7746
gca aaa ctg aga tgg ttc gtt gag aga aac atg gtc aca cca gaa ggg Ala Lys Leu Arg Trp Phe Val Glu Arg Asn Met Val Thr Pro Glu Gly 2555 2560 2565	7794

aaa gta gtg gac ctc ggt tgt ggc aga gga ggc tgg tca tac tat tgt Lys Val Val Asp Leu Gly Cys Gly Arg Gly Gly Trp Ser Tyr Tyr Cys 2570 2575 2580	7842
gga gga cta aag aat gta aga gaa gtc aaa ggc cta aca aaa gga gga Gly Gly Leu Lys Asn Val Arg Glu Val Lys Gly Leu Thr Lys Gly Gly 2585 2590 2595	7890
cca gga cac gaa gaa ccc atc ccc atg tca aca tat ggg tgg aat cta Pro Gly His Glu Glu Pro Ile Pro Met Ser Thr Tyr Gly Trp Asn Leu 2600 2605 2610	7938
gtg cgt ctt caa agt gga gtt gac gtt ttc ttc atc ccg cca gaa aag Val Arg Leu Gln Ser Gly Val Asp Val Phe Phe Ile Pro Pro Glu Lys 2615 2620 2625 2630	7986
tgt gac aca tta ttg tgt gac ata ggg gag tca tca cca aat ccc aca Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro Thr 2635 2640 2645	8034
gtg gaa gca gga cga aca ctc aga gtc ctt aac tta gta gaa aat tgg Val Glu Ala Gly Arg Thr Leu Arg Val Leu Asn Leu Val Glu Asn Trp 2650 2655 2660	8082
ttg aac aac aac act caa ttt tgc ata aag gtt ctc aac cca tat atg Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys Val Leu Asn Pro Tyr Met 2665 2670 2675	8130
ccc tca gtc ata gaa aaa atg gaa gca cta caa agg aaa tat gga gga Pro Ser Val Ile Glu Lys Met Glu Ala Leu Gln Arg Lys Tyr Gly Gly 2680 2685 2690	8178
gcc tta gtg agg aat cca ctc tca cga aac tcc aca cat gag atg tac Ala Leu Val Arg Asn Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr 2695 2700 2705 2710	8226
tgg gta tcc aat gct tcc ggg aac ata gtg tca tca gtg aac atg att Trp Val Ser Asn Ala Ser Gly Asn Ile Val Ser Ser Val Asn Met Ile 2715 2720 2725	8274
tca agg atg ttg atc aac aga ttt aca atg aga tac aag aaa gcc act Ser Arg Met Leu Ile Asn Arg Phe Thr Met Arg Tyr Lys Lys Ala Thr 2730 2735 2740	8322
tac gag ccg gat gtt gac ctc gga agc gga acc cgt aac atc ggg att Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly Thr Arg Asn Ile Gly Ile 2745 2750 2755	8370
gaa agt gag ata cca aac cta gat ata att ggg aaa aga ata gaa aaa Glu Ser Glu Ile Pro Asn Leu Asp Ile Ile Gly Lys Arg Ile Glu Lys 2760 2765 2770	8418

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ata aag caa gag cat gaa aca tca tgg cac tat gac caa gac cac cca Ile Lys Gln Glu His Glu Thr Ser Trp His Tyr Asp Gln Asp His Pro 2775 2780 2785 2790	8466
tac aaa acg tgg gca tac cat ggt agc tat gaa aca aaa cag act gga Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly 2795 2800 2805	8514
tca gca tca tcc atg gtc aac gga gtg gtc agg ctg ctg aca aaa cct Ser Ala Ser Ser Met Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro 2810 2815 2820	8562
tgg gac gtc gtc ccc atg gtg aca cag atg gca atg aca gac acg act Trp Asp Val Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr 2825 2830 2835	8610
cca ttt gga caa cag cgc gtt ttt aaa gag aaa gtg gac acg aga acc Pro Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr 2840 2845 2850	8658
caa gaa ccg aaa gaa ggc acg aag aaa cta atg aaa ata aca gca gag Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu Met Lys Ile Thr Ala Glu 2855 2860 2865 2870	8706
tgg ctt tgg aaa gaa tta ggg aag aaa aag aca ccc agg atg tgc acc Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys Thr Pro Arg Met Cys Thr 2875 2880 2885	8754
aga gaa gaa ttc aca aga aag gtg aga agc aat gca gcc ttg ggg gcc Arg Glu Glu Phe Thr Arg Lys Val Arg Ser Asn Ala Ala Leu Gly Ala 2890 2895 2900	8802
ata ttc act gat gag aac aag tgg aag tcg gca cgt gag gct gtt gaa Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser Ala Arg Glu Ala Val Glu 2905 2910 2915	8850
gat agt agg ttt tgg gag ctg gtt gac aag gaa agg aat ctc cat ctt Asp Ser Arg Phe Trp Glu Leu Val Asp Lys Glu Arg Asn Leu His Leu 2920 2925 2930	8898
gaa gga aag tgt gaa aca tgt gtg tac aac atg atg gga aaa aga gag Glu Gly Lys Cys Glu Thr Cys Val Tyr Asn Met Met Gly Lys Arg Glu 2935 2940 2945 2950	8946
aag aag cta ggg gaa ttc ggc aag gca aaa ggc agc aga gcc ata tgg Lys Lys Leu Gly Glu Phe Gly Lys Ala Lys Gly Ser Arg Ala Ile Trp 2955 2960 2965	8994
tac atg tgg ctt gga gca cgc ttc tta gag ttt gaa gcc cta gga ttc Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu Phe Glu Ala Leu Gly Phe 2970 2975 2980	9042
tta aat gaa gat cac tgg ttc tcc aga gag aac tcc ctg agt gga gtg Leu Asn Glu Asp His Trp Phe Ser Arg Glu Asn Ser Leu Ser Gly Val 2985 2990 2995	9090

gaa gga gaa ggg ctg cac aag cta ggt tac att cta aga gac gtg agc Glu Gly Glu Gly Leu His Lys Leu Gly Tyr Ile Leu Arg Asp Val Ser 3000 3005 3010	9138
aag aaa gag gga gga gca atg tat gcc gat gac acc gca gga tgg gat Lys Lys Glu Gly Gly Ala Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp 3015 3020 3025 3030	9186
aca aga atc aca cta gaa gac cta aaa aat gaa gaa atg gta aca aac Thr Arg Ile Thr Leu Glu Asp Leu Lys Asn Glu Glu Met Val Thr Asn 3035 3040 3045	9234
cac atg gaa gga gaa cac aag aaa cta gcc gag gcc att ttc aaa cta His Met Glu Gly Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu 3050 3055 3060	9282
acg tac caa aac aag gtg gtg cgt gtg caa aga cca aca cca aga ggc Thr Tyr Gln Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly 3065 3070 3075	9330
aca gta atg gac atc ata tcg aga aga gac caa aga ggt agt gga caa Thr Val Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly Gln 3080 3085 3090	9378
gtt ggc acc tat gga ctc aat act ttc acc aat atg gaa gcc caa cta Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu 3095 3100 3105 3110	9426
atc aga cag atg gag gga gaa gga gtc ttt aaa agc att cag cac cta Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile Gln His Leu 3115 3120 3125	9474
aca atc aca gaa gaa atc gct gtg caa aac tgg tta gca aga gtg ggg Thr Ile Thr Glu Glu Ile Ala Val Gln Asn Trp Leu Ala Arg Val Gly 3130 3135 3140	9522
cgc gaa agg tta tca aga atg gcc atc agt gga gat gat tgt gtt gtg Arg Glu Arg Leu Ser Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val 3145 3150 3155	9570
aaa cct tta gat gac agg ttc gca agc gct tta aca gct cta aat gac Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala Leu Thr Ala Leu Asn Asp 3160 3165 3170	9618
atg gga aag att agg aaa gac ata caa caa tgg gaa cct tca aga gga Met Gly Lys Ile Arg Lys Asp Ile Gln Gln Trp Glu Pro Ser Arg Gly 3175 3180 3185 3190	9666
tgg aat gat tgg aca caa gtg ccc ttc tgt tca cac cat ttc cat gag Trp Asn Asp Trp Thr Gln Val Pro Phe Cys Ser His His Phe His Glu 3195 3200 3205	9714

65

tta atc atg aaa gac ggt cgc gta ctc gtt gtt cca tgt aga aac caa Leu Ile Met Lys Asp Gly Arg Val Leu Val Val Pro Cys Arg Asn Gln 3210 3215 3220	9762
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tgc tgc gca gta cca tca cat tgg gtt cca aca agt cga aca acc tgg Cys Ser Ala Val Pro Ser His Trp Val Pro Thr Ser Arg Thr Thr Trp 3275 3280 3285	9954
tcc ata cat gct aaa cat gaa tgg atg aca acg gaa gac atg ctg aca Ser Ile His Ala Lys His Glu Trp Met Thr Thr Glu Asp Met Leu Thr 3290 3295 3300	10002
gtc tgg aac agg gtg tgg att caa gaa aac cca tgg atg gaa gac aaa Val Trp Asn Arg Val Trp Ile Gln Glu Asn Pro Trp Met Glu Asp Lys 3305 3310 3315	10050
act cca gtg gaa tca tgg gag gaa atc cca tac ttg ggg aaa aga gaa Thr Pro Val Glu Ser Trp Glu Glu Ile Pro Tyr Leu Gly Lys Arg Glu 3320 3325 3330	10098
gac caa tgg tgc ggc tca ttg att ggg tta aca agc agg gcc acc tgg Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala Thr Trp 3335 3340 3345 3350	10146
gca aag aac atc caa gca gca ata aat caa gtt aga tcc ctt ata ggc Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln Val Arg Ser Leu Ile Gly 3355 3360 3365	10194
aat gaa gaa tac aca gat tac atg cca tcc atg aaa aga ttc aga aga Asn Glu Glu Tyr Thr Asp Tyr Met Pro Ser Met Lys Arg Phe Arg Arg 3370 3375 3380	10242
gaa gag gaa gaa gca gga gtt ctg tgg tag aaagcaaaac taacatgaaa Glu Glu Glu Glu Ala Gly Val Leu Trp 3385 3390	10292
caaggctaga agtcaggctg gattaagcca tagtacggaa aaaactatgc tacctgtgag ccccgtccaa ggacgttaaa agaagtcagg ccatcataaa tgccatagct tgagtaaact atgcagcctg tagctccacc tgagaaggtg taaaaaatcc gggaggccac aaaccatgga agctgtacgc atggcgtagt ggactagcgg ttagaggaga cccctccctt acaaatcgca gcaacaatgg gggcccgaagg cgagatgaag ctgtagtctc gctggaagga ctagaggtta gaggagacc ccccgaaaca aaaaacagca tattgacgct gggaaagacc agagatcctg ctgtctctc agcatcatc caggcacaga acgccagaaa atggaatggt gctgttgtaat	10352 10412 10472 10532 10592 10652 10712

caacaggttc t

10723

<210> 6
 <211> 3391
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:/Note =
 synthetic construct

<400> 6
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 1 5 10 15
 Lys Arg Ala Arg Asn Arg Val Ser Thr Val Ser Gln Leu Ala Lys Arg
 20 25 30
 Phe Ser Lys Gly Leu Leu Ser Gly Gln Gly Pro Met Lys Leu Val Met
 35 40 45
 Ala Phe Ile Ala Phe Leu Arg Phe Leu Ala Ile Pro Pro Thr Ala Gly
 50 55 60
 Ile Leu Ala Arg Trp Gly Ser Phe Lys Lys Asn Gly Ala Ile Lys Val
 65 70 75 80
 Leu Arg Gly Phe Lys Arg Glu Ile Ser Asn Met Leu Asn Ile Met Asn
 85 90 95
 Arg Arg Lys Arg Ser Val Thr Met Leu Leu Met Leu Leu Pro Thr Ala
 100 105 110
 Leu Ala Phe His Leu Thr Thr Arg Gly Gly Glu Pro His Met Ile Val
 115 120 125
 Ser Lys Gln Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ser Ala Gly
 130 135 140
 Val Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Leu Cys Glu
 145 150 155 160
 Asp Thr Met Thr Tyr Lys Cys Pro Arg Ile Thr Glu Ala Glu Pro Asp
 165 170 175
 Asp Val Asp Cys Trp Cys Asn Ala Thr Asp Thr Trp Val Thr Tyr Gly
 180 185 190
 Thr Cys Ser Gln Thr Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala
 195 200 205
 Leu Ala Pro His Val Gly Leu Gly Leu Glu Thr Arg Ala Glu Thr Trp
 210 215 220
 Met Ser Ser Glu Gly Ala Trp Lys Gln Ile Gln Lys Val Glu Thr Trp
 225 230 235 240
 Ala Leu Arg His Pro Gly Phe Thr Val Ile Ala Leu Phe Leu Ala His
 245 250 255
 Ala Ile Gly Thr Ser Ile Thr Gln Lys Gly Ile Ile Phe Ile Leu Leu
 260 265 270
 Met Leu Val Thr Pro Ser Met Ala Met Arg Cys Val Gly Ile Gly Asn
 275 280 285
 Arg Asp Phe Val Glu Gly Leu Ser Gly Ala Thr Trp Val Asp Val Val
 290 295 300
 Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr
 305 310 315 320

67

Leu Asp Ile Glu	Leu Leu Lys Thr Glu Val Thr Asn Pro Ala Val Leu	325	330	335
Arg Lys Leu Cys Ile Glu Ala Lys Ile Ser Asn Thr Thr Thr Asp Ser		340	345	350
Arg Cys Pro Thr Gln Gly Glu Ala Thr Leu Val Glu Glu Gln Asp Ala		355	360	365
Asn Phe Val Cys Arg Arg Thr Phe Val Asp Arg Gly Trp Gly Asn Gly		370	375	380
Cys Gly Leu Phe Gly Lys Gly Ser Leu Ile Thr Cys Ala Lys Phe Lys		385	390	395
Cys Val Thr Lys Leu Glu Gly Lys Ile Val Gln Tyr Glu Asn Leu Lys		405	410	415
Tyr Ser Val Ile Val Thr Val His Thr Gly Asp Gln His Gln Val Gly		420	425	430
Asn Glu Thr Thr Glu His Gly Thr Thr Ala Thr Ile Thr Pro Gln Ala		435	440	445
Pro Thr Ser Glu Ile Gln Leu Thr Asp Tyr Gly Thr Leu Thr Leu Asp		450	455	460
Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Thr		465	470	475
Met Lys Glu Arg Ser Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu		485	490	495
Pro Leu Pro Trp Thr Ser Gly Ala Ser Thr Ser Gln Glu Thr Trp Asn		500	505	510
Arg Gln Asp Leu Leu Val Thr Phe Lys Thr Ala His Ala Lys Lys Gln		515	520	525
Glu Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu		530	535	540
Thr Gly Ala Thr Glu Ile Gln Thr Ser Gly Thr Thr Thr Ile Phe Ala		545	550	555
Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Thr Leu Lys Gly		565	570	575
Met Ser Tyr Val Met Cys Thr Gly Ser Phe Lys Leu Glu Lys Glu Val		580	585	590
Ala Glu Thr Gln His Gly Thr Val Leu Val Gln Val Lys Tyr Glu Gly		595	600	605
Thr Asp Ala Pro Cys Lys Ile Pro Phe Ser Thr Gln Asp Glu Lys Gly		610	615	620
Ala Thr Gln Asn Gly Arg Leu Ile Thr Ala Asn Pro Ile Val Thr Asp		625	630	635
Lys Glu Lys Pro Val Asn Ile Glu Ala Glu Pro Phe Gly Glu Ser		645	650	655
Tyr Ile Val Val Gly Ala Gly Glu Lys Ala Leu Lys Leu Ser Trp Phe		660	665	670
Lys Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly		675	680	685
Ala Arg Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser		690	695	700
Ile Gly Gly Val Phe Thr Ser Met Gly Lys Leu Val His Gln Val Phe		705	710	715
Gly Thr Ala Tyr Gly Val Leu Phe Ser Gly Val Ser Trp Thr Met Lys		725	730	735
Ile Gly Ile Gly Ile Leu Leu Thr Trp Leu Gly Leu Asn Ser Arg Asn		740	745	750

68

Thr Ser Leu Ser Val Met Cys Ile Ala Ala Gly Ile Val Thr Leu Tyr
 755 760 765
 Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys
 770 775 780
 Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val
 785 790 795 800
 His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys
 805 810 815
 Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile
 820 825 830
 Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro
 835 840 845
 Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met
 850 855 860
 Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg
 865 870 875 880
 Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala
 885 890 895
 Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly
 900 905 910
 Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu
 915 920 925
 Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu
 930 935 940
 Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser
 945 950 955 960
 Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp
 965 970 975
 Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe
 980 985 990
 Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser
 995 1000 1005
 Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala Gly
 1010 1015 1020
 Pro Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr
 1025 1030 1035 1040
 Gly Pro Trp His Leu Gly Lys Leu Glu Met Asp Phe Asp Phe Cys Asp
 1045 1050 1055
 Gly Thr Thr Val Val Val Thr Glu Asp Cys Gly Asn Arg Gly Pro Ser
 1060 1065 1070
 Leu Arg Thr Thr Thr Ala Ser Gly Lys Leu Ile Thr Glu Trp Cys Cys
 1075 1080 1085
 Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr Arg Gly Glu Asp Gly Cys
 1090 1095 1100
 Trp Tyr Gly Met Glu Ile Arg Pro Leu Lys Glu Lys Glu Glu Asn Leu
 1105 1110 1115 1120
 Val Asn Ser Leu Val Thr Ala Gly His Gly Gln Val Asp Asn Phe Ser
 1125 1130 1135
 Leu Gly Val Leu Gly Met Ala Leu Phe Leu Glu Glu Met Leu Arg Thr
 1140 1145 1150
 Arg Val Gly Thr Lys His Ala Ile Leu Leu Val Ala Val Ser Phe Val
 1155 1160 1165
 Thr Leu Ile Thr Gly Asn Met Ser Phe Arg Asp Leu Gly Arg Val Met
 1170 1175 1180

Val Met Val Gly Ala Thr Met Thr Asp Asp Ile Gly Met Gly Val Thr
 1185 1190 1195 1200
 Tyr Leu Ala Leu Leu Ala Ala Phe Lys Val Arg Pro Thr Phe Ala Ala
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 Gly Leu Leu Leu Arg Lys Leu Thr Ser Lys Glu Leu Met Met Thr Thr
 1220 1225 1230
 Ile Gly Ile Val Leu Leu Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu
 1235 1240 1245
 Glu Leu Thr Asp Ala Leu Ala Leu Gly Met Met Val Leu Lys Met Val
 1250 1255 1260
 Arg Asn Met Glu Lys Tyr Gln Leu Ala Val Thr Ile Met Ala Ile Leu
 1265 1270 1275 1280
 Cys Val Pro Asn Ala Val Ile Leu Gln Asn Ala Trp Lys Val Ser Cys
 1285 1290 1295
 Thr Ile Leu Ala Val Val Ser Val Ser Pro Leu Phe Leu Thr Ser Ser
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 Gln Gln Lys Thr Asp Trp Ile Pro Leu Ala Leu Thr Ile Lys Gly Leu
 1315 1320 1325
 Asn Pro Thr Ala Ile Phe Leu Thr Thr Leu Ser Arg Thr Ser Lys Lys
 1330 1335 1340
 Arg Ser Trp Pro Leu Asn Glu Ala Ile Met Ala Val Gly Met Val Ser
 1345 1350 1355 1360
 Ile Leu Ala Ser Ser Leu Leu Lys Asn Asp Ile Pro Met Thr Gly Pro
 1365 1370 1375
 Leu Val Ala Gly Gly Leu Leu Thr Val Cys Tyr Val Leu Thr Gly Arg
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 Ser Ala Asp Leu Glu Leu Glu Arg Ala Ala Asp Val Lys Trp Glu Asp
 1395 1400 1405
 Gln Ala Glu Ile Ser Gly Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser
 1410 1415 1420
 Glu Asp Gly Ser Met Ser Ile Lys Asn Glu Glu Glu Glu Gln Thr Leu
 1425 1430 1435 1440
 Thr Ile Leu Ile Arg Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro
 1445 1450 1455
 Val Ser Ile Pro Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys
 1460 1465 1470
 Lys Gln Arg Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Pro Met
 1475 1480 1485
 Gly Lys Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys Gly
 1490 1495 1500
 Ile Leu Gly Tyr Ser Gln Ile Gly Ala Gly Val Tyr Lys Glu Gly Thr
 1505 1510 1515 1520
 Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu Met His Lys
 1525 1530 1535
 Gly Lys Arg Ile Glu Pro Ser Trp Ala Asp Val Lys Lys Asp Leu Ile
 1540 1545 1550
 Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu Trp Lys Glu Gly Glu
 1555 1560 1565
 Glu Val Gln Val Leu Ala Leu Glu Pro Gly Lys Asn Pro Arg Ala Val
 1570 1575 1580
 Gln Thr Lys Pro Gly Leu Phe Lys Thr Asn Ala Gly Thr Ile Gly Ala
 1585 1590 1595 1600
 Val Ser Leu Asp Phe Ser Pro Gly Thr Ser Gly Ser Pro Ile Ile Asp
 1605 1610 1615

Lys Lys Gly Lys Val Val Gly Leu Tyr Gly Asn Gly Val Val Thr Arg
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 Ser Gly Ala Tyr Val Ser Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu
 1635 1640 1645
 Asp Asn Pro Glu Ile Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr
 1650 1655 1660
 Ile Met Asp Leu His Pro Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro
 1665 1670 1675 1680
 Ala Ile Val Arg Glu Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu
 1685 1690 1695
 Ala Pro Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly
 1700 1705 1710
 Leu Pro Ile Arg Tyr Gln Thr Pro Ala Ile Arg Ala Val His Thr Gly
 1715 1720 1725
 Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg Leu
 1730 1735 1740
 Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu
 1745 1750 1755 1760
 Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser
 1765 1770 1775
 Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe Met Thr Ala Thr
 1780 1785 1790
 Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser Asn Ala Pro Ile Ile
 1795 1800 1805
 Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser Trp Asn Ser Gly His Glu
 1810 1815 1820
 Trp Val Thr Asp Phe Lys Gly Lys Thr Val Trp Phe Val Pro Ser Ile
 1825 1830 1835 1840
 Lys Ala Gly Asn Asp Ile Ala Ala Cys Leu Arg Lys Asn Gly Lys Lys
 1845 1850 1855
 Val Ile Gln Leu Ser Arg Lys Thr Phe Asp Ser Glu Tyr Val Lys Thr
 1860 1865 1870
 Arg Thr Asn Asp Trp Asp Phe Val Val Thr Thr Asp Ile Ser Glu Met
 1875 1880 1885
 Gly Ala Asn Phe Lys Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met
 1890 1895 1900
 Lys Pro Val Ile Leu Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly
 1905 1910 1915 1920
 Pro Met Pro Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile
 1925 1930 1935
 Gly Arg Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu
 1940 1945 1950
 Pro Leu Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met
 1955 1960 1965
 Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met Phe
 1970 1975 1980
 Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu
 1985 1990 1995 2000
 Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg Arg Gly Asp
 2005 2010 2015
 Leu Pro Val Trp Leu Ala Tyr Arg Val Ala Ala Glu Gly Ile Asn Tyr
 2020 2025 2030
 Ala Asp Arg Arg Trp Cys Phe Asp Gly Val Lys Asn Asn Gln Ile Leu
 2035 2040 2045

Glu Glu Asn Val Glu Val Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys
 2050 2055 2060
 Lys Leu Lys Pro Arg Trp Leu Asp Ala Arg Ile Tyr Ser Asp Pro Leu
 2065 2070 2075 2080
 Ala Leu Lys Glu Phe Lys Glu Phe Ala Ala Gly Arg Lys Ser Leu Thr
 2085 2090 2095
 Leu Asn Leu Ile Thr Glu Met Gly Arg Leu Pro Thr Phe Met Thr Gln
 2100 2105 2110
 Lys Ala Arg Asp Ala Leu Asp Asn Leu Ala Val Leu His Thr Ala Glu
 2115 2120 2125
 Ala Gly Gly Arg Ala Tyr Asn His Ala Leu Ser Glu Leu Pro Glu Thr
 2130 2135 2140
 Leu Glu Thr Leu Leu Leu Thr Leu Leu Ala Thr Val Thr Gly Gly
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 Ile Phe Leu Phe Leu Met Ser Ala Arg Gly Ile Gly Lys Met Thr Leu
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 Thr Met Ala Asn Glu Met Gly Phe Leu Glu Lys Thr Lys Lys Asp Leu
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 Gly Leu Gly Ser Ile Ala Thr Gln Gln Pro Glu Ser Asn Ile Leu Asp
 2260 2265 2270
 Ile Asp Leu Arg Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr
 2275 2280 2285
 Thr Phe Val Thr Pro Met Leu Arg His Ser Ile Glu Asn Ser Ser Val
 2290 2295 2300
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 2370 2375 2380
 Met Lys Asn Pro Thr Val Asp Gly Ile Thr Val Ile Asp Leu Asp Pro
 2385 2390 2395 2400
 Ile Pro Tyr Asp Pro Lys Phe Glu Lys Gln Leu Gly Gln Val Met Leu
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 Leu Val Leu Cys Val Thr Gln Val Leu Met Met Arg Thr Thr Trp Ala
 2420 2425 2430
 Leu Cys Glu Ala Leu Thr Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp
 2435 2440 2445
 Glu Gly Asn Pro Gly Arg Phe Trp Asn Thr Thr Ile Ala Val Ser Met
 2450 2455 2460
 Ala Asn Ile Phe Arg Gly Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe
 2465 2470 2475 2480

Ser Ile Met Lys Asn Thr Thr Asn Thr Arg Arg Gly Thr Gly Asn Ile
 2485 2490 2495
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 2500 2505 2510
 Lys Ser Glu Phe Gln Ile Tyr Lys Lys Ser Gly Ile Gln Glu Val Asp
 2515 2520 2525
 Arg Thr Leu Ala Lys Glu Gly Ile Lys Arg Gly Glu Thr Asp His His
 2530 2535 2540
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 2545 2550 2555 2560
 Met Val Thr Pro Glu Gly Lys Val Val Asp Leu Gly Cys Gly Arg Gly
 2565 2570 2575
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 2580 2585 2590
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 2595 2600 2605
 Thr Tyr Gly Trp Asn Leu Val Arg Leu Gln Ser Gly Val Asp Val Phe
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 Phe Ile Pro Pro Glu Lys Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu
 2625 2630 2635 2640
 Ser Ser Pro Asn Pro Thr Val Glu Ala Gly Arg Thr Leu Arg Val Leu
 2645 2650 2655
 Asn Leu Val Glu Asn Trp Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys
 2660 2665 2670
 Val Leu Asn Pro Tyr Met Pro Ser Val Ile Glu Lys Met Glu Ala Leu
 2675 2680 2685
 Gln Arg Lys Tyr Gly Gly Ala Leu Val Arg Asn Pro Leu Ser Arg Asn
 2690 2695 2700
 Ser Thr His Glu Met Tyr Trp Val Ser Asn Ala Ser Gly Asn Ile Val
 2705 2710 2715 2720
 Ser Ser Val Asn Met Ile Ser Arg Met Leu Ile Asn Arg Phe Thr Met
 2725 2730 2735
 Arg Tyr Lys Lys Ala Thr Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly
 2740 2745 2750
 Thr Arg Asn Ile Gly Ile Glu Ser Glu Ile Pro Asn Leu Asp Ile Ile
 2755 2760 2765
 Gly Lys Arg Ile Glu Lys Ile Lys Gln Glu His Glu Thr Ser Trp His
 2770 2775 2780
 Tyr Asp Gln Asp His Pro Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr
 2785 2790 2795 2800
 Glu Thr Lys Gln Thr Gly Ser Ala Ser Ser Met Val Asn Gly Val Val
 2805 2810 2815
 Arg Leu Leu Thr Lys Pro Trp Asp Val Val Pro Met Val Thr Gln Met
 2820 2825 2830
 Ala Met Thr Asp Thr Thr Pro Phe Gly Gln Gln Arg Val Phe Lys Glu
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 Lys Val Asp Thr Arg Thr Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu
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 Met Lys Ile Thr Ala Glu Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys
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 Thr Pro Arg Met Cys Thr Arg Glu Glu Phe Thr Arg Lys Val Arg Ser
 2885 2890 2895
 Asn Ala Ala Leu Gly Ala Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser
 2900 2905 2910

Ala Arg Glu Ala Val Glu Asp Ser Arg Phe Trp Glu Leu Val Asp Lys
 2915 2920 2925
 Glu Arg Asn Leu His Leu Glu Gly Lys Cys Glu Thr Cys Val Tyr Asn
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 Gly Ser Arg Ala Ile Trp Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu
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 Phe Glu Ala Leu Gly Phe Leu Asn Glu Asp His Trp Phe Ser Arg Glu
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 Ile Leu Arg Asp Val Ser Lys Lys Glu Gly Gly Ala Met Tyr Ala Asp
 3010 3015 3020
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 Glu Glu Met Val Thr Asn His Met Glu Gly Glu His Lys Lys Leu Ala
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 Glu Ala Ile Phe Lys Leu Thr Tyr Gln Asn Lys Val Val Arg Val Gln
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 Arg Pro Thr Pro Arg Gly Thr Val Met Asp Ile Ile Ser Arg Arg Asp
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 Gln Arg Gly Ser Gly Gln Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr
 3090 3095 3100
 Asn Met Glu Ala Gln Leu Ile Arg Gln Met Glu Gly Glu Gly Val Phe
 3105 3110 3115 3120
 Lys Ser Ile Gln His Leu Thr Ile Thr Glu Ile Ala Val Gln Asn
 3125 3130 3135
 Trp Leu Ala Arg Val Gly Arg Glu Arg Leu Ser Arg Met Ala Ile Ser
 3140 3145 3150
 Gly Asp Asp Cys Val Val Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala
 3155 3160 3165
 Leu Thr Ala Leu Asn Asp Met Gly Lys Ile Arg Lys Asp Ile Gln Gln
 3170 3175 3180
 Trp Glu Pro Ser Arg Gly Trp Asn Asp Trp Thr Gln Val Pro Phe Cys
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 Val Pro Cys Arg Asn Gln Asp Glu Leu Ile Gly Arg Ala Arg Ile Ser
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 Tyr Ala Gln Met Trp Ser Leu Met Tyr Phe His Arg Arg Asp Leu Arg
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 3265 3270 3275 3280
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 3300 3305 3310
 Pro Trp Met Glu Asp Lys Thr Pro Val Glu Ser Trp Glu Glu Ile Pro
 3315 3320 3325
 Tyr Leu Gly Lys Arg Glu Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu
 3330 3335 3340

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Thr	Ser	Arg	Ala	Thr	Trp	Ala	Lys	Asn	Ile	Gln	Ala	Ala	Ile	Asn	Gln	
3345						3350				3355					3360	
Val	Arg	Ser	Leu	Ile	Gly	Asn	Glu	Glu	Tyr	Thr	Asp	Tyr	Met	Pro	Ser	
			3365						3370						3375	
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<211> 10723

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<221> CDS

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				Met	Ile	
				1	Asn	
					Gln	
					Arg	
					Lys	
					5	

aag	acg	ggt	cga	ccg	tct	ttc	aat	atg	ctg	aaa	cgc	gcg	aga	aac	cgc	162
Lys	Thr	Gly	Arg	Pro	Ser	Phe	Asn	Met	Leu	Lys	Arg	Ala	Arg	Asn	Arg	
		10						15					20			

gtg	tca	act	gtt	tca	cag	ttg	gcg	aag	aga	ttc	tca	aaa	gga	ttg	ctc	210
Val	Ser	Thr	Val	Ser	Gln	Leu	Ala	Lys	Arg	Phe	Ser	Lys	Gly	Leu	Leu	
		25				30						35				

tca	ggc	caa	gga	ccc	atg	aaa	ttg	gtg	atg	gct	ttc	ata	gca	ttc	tta	258
Ser	Gly	Gln	Gly	Pro	Met	Lys	Leu	Val	Met	Ala	Phe	Ile	Ala	Phe	Leu	
		40				45				50						

aga	ttt	cta	gcc	ata	ccc	cca	aca	gca	gga	att	ttg	gct	aga	tgg	ggc	306
Arg	Phe	Leu	Ala	Ile	Pro	Pro	Thr	Ala	Gly	Ile	Leu	Ala	Arg	Trp	Gly	
	55				60				65					70		

tca	ttc	aag	aag	aat	gga	gcg	att	aaa	gtg	tta	cgg	ggt	ttc	aag	aga	354
Ser	Phe	Lys	Lys		Asn	Gly	Ala	Ile	Lys	Val	Leu	Arg	Gly	Phe	Lys	
				75					80					85		

gaa	atc	tca	aac	atg	cta	aac	ata	atg	aac	agg	agg	aaa	aga	tcc	gtg	402
Glu	Ile	Ser	Asn	Met	Leu	Asn	Ile	Met	Asn	Arg	Arg	Lys	Arg	Ser	Val	
			90					95					100			

acc	atg	ctc	ctt	atg	ctg	ctg	ccc	aca	gcc	ctg	gcg	ttc	cat	ctg	acg	450
Thr	Met	Leu	Leu	Met	Leu	Leu	Pro	Thr	Ala	Leu	Ala	Phe	His	Leu	Thr	
			105				110						115			

75

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att gcg atg gat ttg gga gag ttg tgt gag gac acg atg acc tac aaa Ile Ala Met Asp Leu Gly Glu Leu Cys Glu Asp Thr Met Thr Tyr Lys 155 160 165	594
tgc ccc cgg atc act gag gcg gaa cca gat gac gtt gac tgt tgg tgc Cys Pro Arg Ile Thr Glu Ala Glu Pro Asp Asp Val Asp Cys Trp Cys 170 175 180	642
aat gcc acg gac aca tgg gtg acc tat gga acg tgc tct caa act ggc Asn Ala Thr Asp Thr Trp Val Thr Tyr Gly Thr Cys Ser Gln Thr Gly 185 190 195	690
gaa cac cga cga gac aaa cgt tcc gtc gca ttg gcc cca cac gtg ggg Glu His Arg Arg Asp Lys Arg Ser Val Ala Leu Ala Pro His Val Gly 200 205 210	738
ctt ggc cta gaa aca aga gcc gaa acg tgg atg tcc tct gaa ggt gct Leu Gly Leu Glu Thr Arg Ala Glu Thr Trp Met Ser Ser Glu Gly Ala 215 220 225 230	786
tgg aaa cag ata caa aaa gta gag act tgg gct ctg aga cat cca gga Trp Lys Gln Ile Gln Lys Val Glu Thr Trp Ala Leu Arg His Pro Gly 235 240 245	834
ttc acg gtg ata gcc ctt ttt cta gca cat gcc ata gga aca tcc atc Phe Thr Val Ile Ala Leu Phe Leu Ala His Ala Ile Gly Thr Ser Ile 250 255 260	882
acc cag aaa ggg atc att ttc att ttg ctg atg ctg gta aca cca tct Thr Gln Lys Gly Ile Ile Phe Ile Leu Leu Met Leu Val Thr Pro Ser 265 270 275	930
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gct aaa ata tca aac acc acc acc gat tcg aga tgt cca aca caa gga Ala Lys Ile Ser Asn Thr Thr Asp Ser Arg Cys Pro Thr Gln Gly 345 350 355	1170
gaa gcc aca ctg gtg gaa gaa caa gac gcg aac ttt gtg tgc cga cga Glu Ala Thr Leu Val Glu Glu Gln Asp Ala Asn Phe Val Cys Arg Arg 360 365 370	1218
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ggt agt cta ata acg tgt gcc aag ttt aag tgt gtg aca aaa cta gaa Gly Ser Leu Ile Thr Cys Ala Lys Phe Lys Cys Val Thr Lys Leu Glu 395 400 405	1314
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gtc cac act gga gat cag cac cag gtg gga aat gag act aca gaa cat Val His Thr Gly Asp Gln His Gln Val Gly Asn Glu Thr Thr Glu His 425 430 435	1410
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81

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cca ttt cct cag agc aat gca cca atc ata gat gaa gaa aga gaa atc Pro Phe Pro Gln Ser Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu Ile 1800 1805 1810	5538
cct gaa cgc tcg tgg aat tcc gga cat gaa tgg gtc acg gat ttt aaa Pro Glu Arg Ser Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe Lys 1815 1820 1825 1830	5586
ggg aag act gtt tgg ttc gtt cca agt ata aaa gca gga aat gat ata Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile 1835 1840 1845	5634

83

gca gct tgc ctg agg aaa aat gga aag aaa gtg ata caa ctc agt agg Ala Ala Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg 1850 1855 1860	5682
aag acc ttt gat tct gag tat gtc aag act aga acc aat gat tgg gac Lys Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp 1865 1870 1875	5730
ttc gtg gtt aca act gac att tca gaa atg ggt gcc aat ttc aag gct Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys Ala 1880 1885 1890	5778
gag agg gtt ata gac ccc aga cgc tgc atg aaa cca gtc ata cta aca Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile Leu Thr 1895 1900 1905 1910	5826
gat ggt gaa gag cgg gtg att ctg gca gga cct atg cca gtg acc cac Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr His 1915 1920 1925	5874
tct agt gca gca caa aga aga ggg aga ata gga aga aat cca aaa aat Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro Lys Asn 1930 1935 1940	5922
gag aat gac cag tac ata tac atg ggg gaa cct ctg gaa aat gat gaa Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro Leu Glu Asn Asp Glu 1945 1950 1955	5970
gac tgt gca cac tgg aaa gaa gct aaa atg ctc cta gat aac atc aac Asp Cys Ala His Trp Lys Glu Ala Lys Met Leu Leu Asp Asn Ile Asn 1960 1965 1970	6018
acg cca gaa gga atc att cct agc atg ttc gaa cca gag cgt gaa aag Thr Pro Glu Gly Ile Ile Pro Ser Met Phe Glu Pro Glu Arg Glu Lys 1975 1980 1985 1990	6066
gtg gat gcc att gat ggc gaa tac cgc ttg aga gga gaa gca agg aaa Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu Arg Gly Glu Ala Arg Lys 1995 2000 2005	6114
acc ttt gta gac tta atg aga aga gga gac cta cca gtc tgg ttg gcc Thr Phe Val Asp Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ala 2010 2015 2020	6162
tac aga gtg gca gct gaa ggc atc aac tac gca gac aga agg tgg tgt Tyr Arg Val Ala Ala Glu Gly Ile Asn Tyr Ala Asp Arg Arg Trp Cys 2025 2030 2035	6210
ttt gat gga gtc aag aac aac caa atc cta gaa gaa aac gtg gaa gtt Phe Asp Gly Val Lys Asn Asn Gln Ile Leu Glu Glu Asn Val Glu Val 2040 2045 2050	6258
gaa atc tgg aca aaa gaa ggg gaa agg aag aaa ttg aaa ccc aga tgg Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp 2055 2060 2065 2070	6306

84

ttg gat gct agg atc tat tct gac cca ctg gcg cta aaa gaa ttt aag Leu Asp Ala Arg Ile Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys 2075 2080 2085	6354
gaa ttt gca gcc gga aga aag tct ctg acc ctg aac cta atc aca gaa Glu Phe Ala Ala Gly Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu 2090 2095 2100	6402
atg ggt agg ctc cca acc ttc atg act cag aag gca aga gac gca ctg Met Gly Arg Leu Pro Thr Phe Met Thr Gln Lys Ala Arg Asp Ala Leu 2105 2110 2115	6450
gac aac tta gca gtg ctg cac acg gct gag gca ggt gga agg gcg tac Asp Asn Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala Tyr 2120 2125 2130	6498
aac cat gct ctc agt gaa ctg ccg gag acc ctg gag aca ttg ctt tta Asn His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu Leu Leu 2135 2140 2145 2150	6546
ctg aca ctt ctg gct aca gtc acg gga ggg atc ttt tta ttc ttg atg Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu Phe Leu Met 2155 2160 2165	6594
agc gca agg ggc ata ggg aag atg acc ctg gga atg tgc tgc ata atc Ser Ala Arg Gly Ile Gly Lys Met Thr Leu Gly Met Cys Cys Ile Ile 2170 2175 2180	6642
acg gct agc atc ctc cta tgg tac gca caa ata cag cca cac tgg ata Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln Ile Gln Pro His Trp Ile 2185 2190 2195	6690
gca gct tca ata ata ctg gag ttt ttt ctc ata gtt ttg ctt att cca Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Ile Val Leu Leu Ile Pro 2200 2205 2210	6738
gaa cct gaa aaa cag aga aca ccc caa gac aac caa ctg acc tac gtt Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn Gln Leu Thr Tyr Val 2215 2220 2225 2230	6786
gtc ata gcc atc ctc aca gtg gtg gcc gca acc atg gca aac gag atg Val Ile Ala Ile Leu Thr Val Val Ala Ala Thr Met Ala Asn Glu Met 2235 2240 2245	6834
ggt ttc cta gaa aaa acg aag aaa gat ctc gga ttg gga agc att gca Gly Phe Leu Glu Lys Thr Lys Lys Asp Leu Gly Leu Gly Ser Ile Ala 2250 2255 2260	6882
acc cag caa ccc gag agc aac atc ctg gac ata gat cta cgt cct gca Thr Gln Gln Pro Glu Ser Asn Ile Leu Asp Ile Asp Leu Arg Pro Ala 2265 2270 2275	6930

85

tca gca tgg acg ctg tat gcc gtg gcc aca aca ttt gtt aca cca atg Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Phe Val Thr Pro Met 2280 2285 2290	6978
ttg aga cat agc att gaa aat tcc tca gtg aat gtg tcc cta aca gct Leu Arg His Ser Ile Glu Asn Ser Ser Val Asn Val Ser Leu Thr Ala 2295 2300 2305 2310	7026
ata gcc aac caa gcc aca gtg tta atg ggt ctc ggg aaa gga tgg cca Ile Ala Asn Gln Ala Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro 2315 2320 2325	7074
ttg tca aag atg gac atc gga gtt ccc ctt ctc gcc att gga tgc tac Leu Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala Ile Gly Cys Tyr 2330 2335 2340	7122
tca caa gtc aac ccc ata act ctc aca gca gct ctt ttc tta ttg gta Ser Gln Val Asn Pro Ile Thr Leu Thr Ala Ala Leu Phe Leu Leu Val 2345 2350 2355	7170
gca cat tat gcc atc ata ggg cca gga ctc caa gca aaa gca acc aga Ala His Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg 2360 2365 2370	7218
gaa gct cag aaa aga gca gcg gcg ggc atc atg aaa aac cca act gtc Glu Ala Gln Lys Arg Ala Ala Ala Gly Ile Met Lys Asn Pro Thr Val 2375 2380 2385 2390	7266
gat gga ata aca gtg att gac cta gat cca ata cct tat gat cca aag Asp Gly Ile Thr Val Ile Asp Leu Asp Pro Ile Pro Tyr Asp Pro Lys 2395 2400 2405	7314
ttt gaa aag cag ttg gga caa gta atg ctc cta gtc ctc tgc gtg act Phe Glu Lys Gln Leu Gly Gln Val Met Leu Leu Val Leu Cys Val Thr 2410 2415 2420	7362
caa gta ttg atg atg agg act aca tgg gct ctg tgt gag gct tta acc Gln Val Leu Met Met Arg Thr Thr Trp Ala Leu Cys Glu Ala Leu Thr 2425 2430 2435	7410
tta gct acc ggg ccc atc tcc aca ttg tgg gaa gga aat cca ggg agg Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp Glu Gly Asn Pro Gly Arg 2440 2445 2450	7458
ttt tgg aac act acc att gcg gtg tca atg gct aac att ttt aga ggg Phe Trp Asn Thr Thr Ile Ala Val Ser Met Ala Asn Ile Phe Arg Gly 2455 2460 2465 2470	7506
agt tac ttg gcc gga gct gga ctt ctc ttt tct att atg aag aac aca Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe Ser Ile Met Lys Asn Thr 2475 2480 2485	7554
acc aac aca aga agg gga act ggc aac ata gga gag acg ctt gga gag Thr Asn Thr Arg Arg Gly Thr Gly Asn Ile Gly Glu Thr Leu Gly Glu 2490 2495 2500	7602

aaa tgg aaa agc cga ttg aac gca ttg gga aaa agt gaa ttc cag atc Lys Trp Lys Ser Arg Leu Asn Ala Leu Gly Lys Ser Glu Phe Gln Ile 2505 2510 2515	7650
tac aag aaa agt gga atc cag gaa gtg gat aga acc tta gca aaa gaa Tyr Lys Lys Ser Gly Ile Gln Glu Val Asp Arg Thr Leu Ala Lys Glu 2520 2525 2530	7698
ggc att aaa aga gga gaa acg gac cat cac gct gtg tgg cga ggc tca Gly Ile Lys Arg Gly Glu Thr Asp His His Ala Val Ser Arg Gly Ser 2535 2540 2545 2550	7746
gca aaa ctg aga tgg ttc gtt gag aga aac atg gtc aca cca gaa ggg Ala Lys Leu Arg Trp Phe Val Glu Arg Asn Met Val Thr Pro Glu Gly 2555 2560 2565	7794
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cca gga cac gaa gaa ccc atc ccc atg tca aca tat ggg tgg aat cta Pro Gly His Glu Glu Pro Ile Pro Met Ser Thr Tyr Gly Trp Asn Leu 2600 2605 2610	7938
gtg cgt ctt caa agt gga gtt gac gtt ttc ttc atc ccg cca gaa aag Val Arg Leu Gln Ser Gly Val Asp Val Phe Phe Ile Pro Pro Glu Lys 2615 2620 2625 2630	7986
tgt gac aca tta ttg tgt gac ata ggg gag tca tca cca aat ccc aca Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro Thr 2635 2640 2645	8034
gtg gaa gca gga cga aca ctc aga gtc ctt aac tta gta gaa aat tgg Val Glu Ala Gly Arg Thr Leu Arg Val Leu Asn Leu Val Glu Asn Trp 2650 2655 2660	8082
ttg aac aac aac act caa ttt tgc ata aag gtt ctc aac cca tat atg Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys Val Leu Asn Pro Tyr Met 2665 2670 2675	8130
ccc tca gtc ata gaa aaa atg gaa gca cta caa agg aaa tat gga gga Pro Ser Val Ile Glu Lys Met Glu Ala Leu Gln Arg Lys Tyr Gly Gly 2680 2685 2690	8178
gcc tta gtg agg aat cca ctc tca cga aac tcc aca cat gag atg tac Ala Leu Val Arg Asn Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr 2695 2700 2705 2710	8226

tgg gta tcc aat gct tcc ggg aac ata gtg tca tca gtg aac atg att	8274
Trp Val Ser Asn Ala Ser Gly Asn Ile Val Ser Ser Val Asn Met Ile	
2715 2720 2725	
tca agg atg ttg atc aac aga ttt aca atg aga tac aag aaa gcc act	8322
Ser Arg Met Leu Ile Asn Arg Phe Thr Met Arg Tyr Lys Lys Ala Thr	
2730 2735 2740	
tac gag ccg gat gtt gac ctc gga agc gga acc cgt aac atc ggg att	8370
Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly Thr Arg Asn Ile Gly Ile	
2745 2750 2755	
gaa agt gag ata cca aac cta gat ata att ggg aaa aga ata gaa aaa	8418
Glu Ser Glu Ile Pro Asn Leu Asp Ile Ile Gly Lys Arg Ile Glu Lys	
2760 2765 2770	
ata aag caa gag cat gaa aca tca tgg cac tat gac caa gac cac cca	8466
Ile Lys Gln Glu His Glu Thr Ser Trp His Tyr Asp Gln Asp His Pro	
2775 2780 2785 2790	
tac aaa acg tgg gca tac cat ggt agc tat gaa aca aaa cag act gga	8514
Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly	
2795 2800 2805	
tca gca tca tcc atg gtc aac gga gtg gtc agg ctg ctg aca aaa cct	8562
Ser Ala Ser Ser Met Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro	
2810 2815 2820	
tgg gac gtc gtc ccc atg gtg aca cag atg gca atg aca gac acg act	8610
Trp Asp Val Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr	
2825 2830 2835	
cca ttt gga caa cag cgc gtt ttt aaa gag aaa gtg gac acg aga acc	8658
Pro Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr	
2840 2845 2850	
caa gaa ccg aaa gaa ggc acg aag aaa cta atg aaa ata aca gca gag	8706
Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu Met Lys Ile Thr Ala Glu	
2855 2860 2865 2870	
tgg ctt tgg aaa gaa tta ggg aag aaa aag aca ccc agg atg tgc acc	8754
Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys Thr Pro Arg Met Cys Thr	
2875 2880 2885	
aga gaa gaa ttc aca aga aag gtg aga agc aat gca gcc ttg ggg gcc	8802
Arg Glu Glu Phe Thr Arg Lys Val Arg Ser Asn Ala Ala Leu Gly Ala	
2890 2895 2900	
ata ttc act gat gag aac aag tgg aag tcg gca cgt gag gct gtt gaa	8850
Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser Ala Arg Glu Ala Val Glu	
2905 2910 2915	
gat agt agg ttt tgg gag ctg gtt gac aag gaa agg aat ctc cat ctt	8898
Asp Ser Arg Phe Trp Glu Val Asp Lys Glu Arg Asn Leu His Leu	
2920 2925 2930	

gaa gga aag tgt gaa aca tgt gtg tac aac atg atg gga aaa aga gag Glu Gly Lys Cys Glu Thr Cys Val Tyr Asn Met Met Gly Lys Arg Glu 2935 2940 2945 2950	8946
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gaa gga gaa ggg ctg cac aag cta ggt tac att cta aga gac gtg agc Glu Gly Glu Gly Leu His Lys Leu Gly Tyr Ile Leu Arg Asp Val Ser 3000 3005 3010	9138
aag aaa gag gga gga gca atg tat gcc gat gac acc gca gga tgg gat Lys Lys Glu Gly Gly Ala Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp 3015 3020 3025 3030	9186
aca aga atc aca cta gaa gac cta aaa aat gaa gaa atg gta aca aac Thr Arg Ile Thr Leu Glu Asp Leu Lys Asn Glu Glu Met Val Thr Asn 3035 3040 3045	9234
cac atg gaa gga gaa cac aag aaa cta gcc gag gcc att ttc aaa cta His Met Glu Gly Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu 3050 3055 3060	9282
acg tac caa aac aag gtg gtg cgt gtg caa aga cca aca cca aga ggc Thr Tyr Gln Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly 3065 3070 3075	9330
aca gta atg gac atc ata tcg aga aga gac caa aga ggt agt gga caa Thr Val Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly Gln 3080 3085 3090	9378
gtt ggc acc tat gga ctc aat act ttc acc aat atg gaa gcc caa cta Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu 3095 3100 3105 3110	9426
atc aga cag atg gag gga gaa gga gtc ttt aaa agc att cag cac cta Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile Gln His Leu 3115 3120 3125	9474
aca atc aca gaa gaa atc gct gtg caa aac tgg tta gca aga gtg ggg Thr Ile Thr Glu Glu Ile Ala Val Gln Asn Trp Leu Ala Arg Val Gly 3130 3135 3140	9522

cgc gaa agg tta tca aga atg gcc atc agt gga gat gat tgt gtt gtg Arg Glu Arg Leu Ser Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val 3145 3150 3155	9570
aaa cct tta gat gac agg ttc gca agc gct tta aca gct cta aat gac Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala Leu Thr Ala Leu Asn Asp 3160 3165 3170	9618
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tcc ata cat gct aaa cat gaa tgg atg aca acg gaa gac atg ctg aca Ser Ile His Ala Lys His Glu Trp Met Thr Thr Glu Asp Met Leu Thr 3290 3295 3300	10002
gtc tgg aac agg gtg tgg att caa gaa aac cca tgg atg gaa gac aaa Val Trp Asn Arg Val Trp Ile Gln Glu Asn Pro Trp Met Glu Asp Lys 3305 3310 3315	10050
act cca gtg gaa tca tgg gag gaa atc cca tac ttg ggg aaa aga gaa Thr Pro Val Glu Ser Trp Glu Glu Ile Pro Tyr Leu Gly Lys Arg Glu 3320 3325 3330	10098
gac caa tgg tgc ggc tca ttg att ggg tta aca agc agg gcc acc tgg Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala Thr Trp 3335 3340 3345 3350	10146
gca aag aac atc caa gca gca ata aat caa gtt aga tcc ctt ata ggc Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln Val Arg Ser Leu Ile Gly 3355 3360 3365	10194

90

aat gaa gaa tac aca gat tac atg cca tcc atg aaa aga ttc aga aga 10242
 Asn Glu Glu Tyr Thr Asp Tyr Met Pro Ser Met Lys Arg Phe Arg Arg
 3370 3375 3380

gaa gag gaa gaa gca gga gtt ctg tgg tag aaagcaaaac taacatgaaa 10292
 Glu Glu Glu Glu Glu Ala Gly Val Leu Trp *
 3385 3390

caaggctaga agtcaggctcg gattaagcca tagtacggaa aaaactatgc tacctgtgag 10352
 ccccgcccaa ggacgttaaa agaagtcagg ccatacataa tgccatagct tgagtaaact 10412
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 gcaacaatgg gggcccaagg cgagatgaag ctgtagtctc gctggaagga ctagagggtta 10592
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<210> 8

<211> 3391

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
 synthetic construct

<400> 8

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 Lys Arg Ala Arg Asn Arg Val Ser Thr Val Ser Gln Leu Ala Lys Arg
 20 25 30
 Phe Ser Lys Gly Leu Leu Ser Gly Gln Gly Pro Met Lys Leu Val Met
 35 40 45
 Ala Phe Ile Ala Phe Leu Arg Phe Leu Ala Ile Pro Pro Thr Ala Gly
 50 55 60
 Ile Leu Ala Arg Trp Gly Ser Phe Lys Lys Asn Gly Ala Ile Lys Val
 65 70 75 80
 Leu Arg Gly Phe Lys Arg Glu Ile Ser Asn Met Leu Asn Ile Met Asn
 85 90 95
 Arg Arg Lys Arg Ser Val Thr Met Leu Leu Met Leu Leu Pro Thr Ala
 100 105 110
 Leu Ala Phe His Leu Thr Thr Arg Gly Gly Glu Pro His Met Ile Val
 115 120 125
 Ser Lys Gln Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ser Ala Gly
 130 135 140
 Val Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Leu Cys Glu
 145 150 155 160
 Asp Thr Met Thr Tyr Lys Cys Pro Arg Ile Thr Glu Ala Glu Pro Asp
 165 170 175
 Asp Val Asp Cys Trp Cys Asn Ala Thr Asp Thr Trp Val Thr Tyr Gly
 180 185 190
 Thr Cys Ser Gln Thr Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala
 195 200 205

Leu Ala Pro His Val Gly Leu Gly Leu Glu Thr Arg Ala Glu Thr Trp
 210 215 220
 Met Ser Ser Glu Gly Ala Trp Lys Gln Ile Gln Lys Val Glu Thr Trp
 225 230 235 240
 Ala Leu Arg His Pro Gly Phe Thr Val Ile Ala Leu Phe Leu Ala His
 245 250 255
 Ala Ile Gly Thr Ser Ile Thr Gln Lys Gly Ile Ile Phe Ile Leu Leu
 260 265 270
 Met Leu Val Thr Pro Ser Met Ala Met Arg Cys Val Gly Ile Gly Asn
 275 280 285
 Arg Asp Phe Val Glu Gly Leu Ser Gly Ala Thr Trp Val Asp Val Val
 290 295 300
 Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr
 305 310 315 320
 Leu Asp Ile Glu Leu Leu Lys Thr Glu Val Thr Asn Pro Ala Val Leu
 325 330 335
 Arg Lys Leu Cys Ile Glu Ala Lys Ile Ser Asn Thr Thr Thr Asp Ser
 340 345 350
 Arg Cys Pro Thr Gln Gly Glu Ala Thr Leu Val Glu Glu Gln Asp Ala
 355 360 365
 Asn Phe Val Cys Arg Arg Thr Phe Val Asp Arg Gly Trp Gly Asn Gly
 370 375 380
 Cys Gly Leu Phe Gly Lys Gly Ser Leu Ile Thr Cys Ala Lys Phe Lys
 385 390 395 400
 Cys Val Thr Lys Leu Glu Gly Lys Ile Ala Gln Tyr Glu Asn Leu Lys
 405 410 415
 Tyr Ser Val Ile Val Thr Val His Thr Gly Asp Gln His Gln Val Gly
 420 425 430
 Asn Glu Thr Thr Glu His Gly Thr Thr Ala Thr Ile Thr Pro Gln Ala
 435 440 445
 Pro Thr Ser Glu Ile Gln Leu Thr Asp Tyr Gly Thr Leu Thr Leu Asp
 450 455 460
 Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Thr
 465 470 475 480
 Met Lys Lys Lys Ser Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu
 485 490 495
 Pro Leu Pro Trp Thr Ser Gly Ala Leu Thr Ser Gln Glu Thr Trp Asn
 500 505 510
 Arg Gln Asp Leu Leu Val Thr Phe Lys Thr Ala His Ala Lys Lys Gln
 515 520 525
 Glu Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu
 530 535 540
 Thr Gly Ala Thr Glu Ile Gln Thr Ser Gly Thr Thr Thr Ile Phe Ala
 545 550 555 560
 Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Thr Leu Lys Gly
 565 570 575
 Met Ser Tyr Val Met Cys Thr Gly Ser Phe Lys Leu Glu Lys Glu Val
 580 585 590
 Ala Glu Thr Gln His Gly Thr Val Leu Val Gln Val Lys Tyr Glu Gly
 595 600 605
 Thr Asp Ala Pro Cys Lys Ile Pro Phe Ser Thr Gln Asp Glu Lys Gly
 610 615 620
 Ala Thr Gln Asn Gly Arg Leu Ile Thr Ala Asn Pro Ile Val Thr Asp
 625 630 635 640

Lys Glu Lys Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Glu Ser
 645 650 655
 Tyr Ile Val Val Gly Ala Gly Glu Lys Ala Leu Lys Leu Ser Trp Phe
 660 665 670
 Lys Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly
 675 680 685
 Ala Arg Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser
 690 695 700
 Ile Gly Gly Val Phe Thr Ser Met Gly Lys Leu Val His Gln Val Phe
 705 710 715 720
 Gly Thr Ala Tyr Gly Val Leu Phe Ser Gly Val Ser Trp Thr Met Lys
 725 730 735
 Ile Gly Ile Gly Ile Leu Leu Thr Trp Leu Gly Leu Asn Ser Arg Asn
 740 745 750
 Thr Ser Leu Ser Val Met Cys Ile Ala Ala Gly Ile Val Thr Leu Tyr
 755 760 765
 Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys
 770 775 780
 Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val
 785 790 795 800
 His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys
 805 810 815
 Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile
 820 825 830
 Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro
 835 840 845
 Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met
 850 855 860
 Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg
 865 870 875 880
 Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala
 885 890 895
 Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly
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 Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu
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 Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu
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 Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser
 945 950 955 960
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 965 970 975
 Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe
 980 985 990
 Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser
 995 1000 1005
 Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala Gly
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 Pro Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr
 1025 1030 1035 1040
 Gly Pro Trp His Leu Gly Lys Leu Glu Met Asp Phe Asp Phe Cys Asp
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 Gly Thr Thr Val Val Val Thr Glu Asp Cys Gly Asn Arg Gly Pro Ser
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 Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr Arg Gly Glu Asp Gly Cys
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 Leu Gly Val Leu Gly Met Ala Leu Phe Leu Glu Glu Met Leu Arg Thr
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 Arg Val Gly Thr Lys His Ala Ile Leu Leu Val Ala Val Ser Phe Val
 1155 1160 1165
 Thr Leu Ile Thr Gly Asn Met Ser Phe Arg Asp Leu Gly Arg Val Met
 1170 1175 1180
 Val Met Val Gly Ala Thr Met Thr Asp Asp Ile Gly Met Gly Val Thr
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 Tyr Leu Ala Leu Leu Ala Ala Phe Lys Val Arg Pro Thr Phe Ala Ala
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 Gly Leu Leu Leu Arg Lys Leu Thr Ser Lys Glu Leu Met Met Thr Thr Thr
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 Ile Gly Ile Val Leu Leu Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu
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 Glu Leu Thr Asp Ala Leu Ala Leu Gly Met Met Val Leu Lys Met Val
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 Arg Asn Met Glu Lys Tyr Gln Leu Ala Val Thr Ile Met Ala Ile Leu
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 Cys Val Pro Asn Ala Val Ile Leu Gln Asn Ala Trp Lys Val Ser Cys
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 Thr Ile Leu Ala Val Val Ser Val Ser Pro Leu Phe Leu Thr Ser Ser
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 Asn Pro Thr Ala Ile Phe Leu Thr Thr Leu Ser Arg Thr Ser Lys Lys
 1330 1335 1340
 Arg Ser Trp Pro Leu Asn Glu Ala Ile Met Ala Val Gly Met Val Ser
 1345 1350 1355 1360
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 Ser Ala Asp Leu Glu Leu Glu Arg Ala Ala Asp Val Lys Trp Glu Asp
 1395 1400 1405
 Gln Ala Glu Ile Ser Gly Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser
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 1425 1430 1435 1440
 Thr Ile Leu Ile Arg Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro
 1445 1450 1455
 Val Ser Ile Pro Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys
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 Lys Gln Arg Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Met
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 Gly Lys Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys Gly
 1490 1495 1500

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 Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu Met His Lys
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 Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu Trp Lys Glu Gly Glu
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 Val Ser Leu Asp Phe Ser Pro Gly Thr Ser Gly Ser Pro Ile Ile Asp
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 Lys Lys Gly Lys Val Val Gly Leu Tyr Gly Asn Gly Val Val Thr Arg
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 Ser Gly Ala Tyr Val Ser Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu
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 Asp Asn Pro Glu Ile Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr
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 Ile Met Asp Leu His Pro Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro
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 Ala Ile Val Arg Glu Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu
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 Ala Pro Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly
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 Leu Pro Ile Arg Tyr Gln Thr Pro Ala Ile Arg Ala Val His Thr Gly
 1715 1720 1725
 Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg Leu
 1730 1735 1740
 Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu
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 Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser
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 Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe Met Thr Ala Thr
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 Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser Asn Ala Pro Ile Ile
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 Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser Trp Asn Ser Gly His Glu
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 Trp Val Thr Asp Phe Lys Gly Lys Thr Val Trp Phe Val Pro Ser Ile
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 Lys Ala Gly Asn Asp Ile Ala Ala Cys Leu Arg Lys Asn Gly Lys Lys
 1845 1850 1855
 Val Ile Gln Leu Ser Arg Lys Thr Phe Asp Ser Glu Tyr Val Lys Thr
 1860 1865 1870
 Arg Thr Asn Asp Trp Asp Phe Val Val Thr Thr Asp Ile Ser Glu Met
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 Gly Ala Asn Phe Lys Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met
 1890 1895 1900
 Lys Pro Val Ile Leu Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly
 1905 1910 1915 1920
 Pro Met Pro Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile
 1925 1930 1935

Gly Arg Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu
 1940 1945 1950
 Pro Leu Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met
 1955 1960 1965
 Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met Phe
 1970 1975 1980
 Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu
 1985 1990 1995 2000
 Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg Arg Gly Asp
 2005 2010 2015
 Leu Pro Val Trp Leu Ala Tyr Arg Val Ala Ala Glu Gly Ile Asn Tyr
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 Ala Asp Arg Arg Trp Cys Phe Asp Gly Val Lys Asn Asn Gln Ile Leu
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 Lys Leu Lys Pro Arg Trp Leu Asp Ala Arg Ile Tyr Ser Asp Pro Leu
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 Ala Gly Gly Arg Ala Tyr Asn His Ala Leu Ser Glu Leu Pro Glu Thr
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 Leu Glu Thr Leu Leu Leu Thr Leu Leu Ala Thr Val Thr Gly Gly
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 Ile Gln Pro His Trp Ile Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu
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 Gly Leu Gly Ser Ile Ala Thr Gln Gln Pro Glu Ser Asn Ile Leu Asp
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 Ile Asp Leu Arg Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr
 2275 2280 2285
 Thr Phe Val Thr Pro Met Leu Arg His Ser Ile Glu Asn Ser Ser Val
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 2305 2310 2315 2320
 Leu Gly Lys Gly Trp Pro Leu Ser Lys Met Asp Ile Gly Val Pro Leu
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 Leu Ala Ile Gly Cys Tyr Ser Gln Val Asn Pro Ile Thr Leu Thr Ala
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 Ala Leu Phe Leu Leu Val Ala His Tyr Ala Ile Ile Gly Pro Gly Leu
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Gln Ala Lys Ala Thr Arg Glu Ala Gln Lys Arg Ala Ala Ala Gly Ile
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 2385 2390 2395 2400
 Ile Pro Tyr Asp Pro Lys Phe Glu Lys Gln Leu Gly Gln Val Met Leu
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 Leu Cys Glu Ala Leu Thr Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp
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 Glu Gly Asn Pro Gly Arg Phe Trp Asn Thr Thr Ile Ala Val Ser Met
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 Ala Asn Ile Phe Arg Gly Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe
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 Gly Glu Thr Leu Gly Glu Lys Trp Lys Ser Arg Leu Asn Ala Leu Gly
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 Met Val Thr Pro Glu Gly Lys Val Val Asp Leu Gly Cys Gly Arg Gly
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 2580 2585 2590
 Gly Leu Thr Lys Gly Gly Pro Gly His Glu Glu Pro Ile Pro Met Ser
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 Phe Ile Pro Pro Glu Lys Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu
 2625 2630 2635 2640
 Ser Ser Pro Asn Pro Thr Val Glu Ala Gly Arg Thr Leu Arg Val Leu
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 Asn Leu Val Glu Asn Trp Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys
 2660 2665 2670
 Val Leu Asn Pro Tyr Met Pro Ser Val Ile Glu Lys Met Glu Ala Leu
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 Gln Arg Lys Tyr Gly Gly Ala Leu Val Arg Asn Pro Leu Ser Arg Asn
 2690 2695 2700
 Ser Thr His Glu Met Tyr Trp Val Ser Asn Ala Ser Gly Asn Ile Val
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 Ser Ser Val Asn Met Ile Ser Arg Met Leu Ile Asn Arg Phe Thr Met
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 Arg Tyr Lys Lys Ala Thr Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly
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 Thr Arg Asn Ile Gly Ile Glu Ser Glu Ile Pro Asn Leu Asp Ile Ile
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 Gly Lys Arg Ile Glu Lys Ile Lys Gln Glu His Glu Thr Ser Trp His
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 Tyr Asp Gln Asp His Pro Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr
 2785 2790 2795 2800

Glu Thr Lys Gln Thr Gly Ser Ala Ser Ser Met Val Asn Gly Val Val
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 Ala Met Thr Asp Thr Thr Pro Phe Gly Gln Gln Arg Val Phe Lys Glu
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 Lys Val Asp Thr Arg Thr Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu
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 Thr Pro Arg Met Cys Thr Arg Glu Glu Phe Thr Arg Lys Val Arg Ser
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 Glu Glu Met Val Thr Asn His Met Glu Gly Glu His Lys Lys Leu Ala
 3045 3050 3055
 Glu Ala Ile Phe Lys Leu Thr Tyr Gln Asn Lys Val Val Arg Val Gln
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 Arg Pro Thr Pro Arg Gly Thr Val Met Asp Ile Ile Ser Arg Arg Asp
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 Gln Arg Gly Ser Gly Gln Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr
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 Asn Met Glu Ala Gln Leu Ile Arg Gln Met Glu Gly Glu Gly Val Phe
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 Lys Ser Ile Gln His Leu Thr Ile Thr Glu Glu Ile Ala Val Gln Asn
 3125 3130 3135
 Trp Leu Ala Arg Val Gly Arg Glu Arg Leu Ser Arg Met Ala Ile Ser
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 Gly Asp Asp Cys Val Val Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala
 3155 3160 3165
 Leu Thr Ala Leu Asn Asp Met Gly Lys Ile Arg Lys Asp Ile Gln Gln
 3170 3175 3180
 Trp Glu Pro Ser Arg Gly Trp Asn Asp Trp Thr Gln Val Pro Phe Cys
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 Ser His His Phe His Glu Leu Ile Met Lys Asp Gly Arg Val Leu Val
 3205 3210 3215
 Val Pro Cys Arg Asn Gln Asp Glu Leu Ile Gly Arg Ala Arg Ile Ser
 3220 3225 3230

98

Gln Gly Ala Gly Trp Ser Leu Arg Glu Thr Ala Cys Leu Gly Lys Ser
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 Tyr Ala Gln Met Trp Ser Leu Met Tyr Phe His Arg Arg Asp Leu Arg
 3250 3255 3260
 Leu Ala Ala Asn Ala Ile Cys Ser Ala Val Pro Ser His Trp Val Pro
 3265 3270 3275 3280
 Thr Ser Arg Thr Thr Trp Ser Ile His Ala Lys His Glu Trp Met Thr
 3285 3290 3295
 Thr Glu Asp Met Leu Thr Val Trp Asn Arg Val Trp Ile Gln Glu Asn
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 Pro Trp Met Glu Asp Lys Thr Pro Val Glu Ser Trp Glu Glu Ile Pro
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 Tyr Leu Gly Lys Arg Glu Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu
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 Thr Ser Arg Ala Thr Trp Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln
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<223> Description of Artificial Sequence:/Note =
 synthetic construct

<221> CDS

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 Met Asn Asn Gln Arg Lys
 1 5
 aag gcg aaa aac acg cct ttc aat atg ctg aaa cgc gag aga aac cgc 162
 Lys Ala Lys Asn Thr Pro Phe Asn Met Leu Lys Arg Glu Arg Asn Arg
 10 15 20
 gtg tcg act gtg caa cag ctg aca aag aga ttc tca ctt gga atg ctg 210
 Val Ser Thr Val Gln Gln Leu Thr Lys Arg Phe Ser Leu Gly Met Leu
 25 30 35
 cag gga cga gga cca tta aaa ctg ttc atg gcc ctg gtg gcg ttc ctt 258
 Gln Gly Arg Gly Pro Leu Lys Leu Phe Met Ala Leu Val Ala Phe Leu
 40 45 50
 cgt ttc cta aca atc cca cca aca gca ggg ata ttg aag aga tgg gga 306

Arg	Phe	Leu	Thr	Ile	Pro	Pro	Thr	Ala	Gly	Ile	Leu	Lys	Arg	Trp	Gly		
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aca	att	aaa	aaa	tca	aaa	gct	att	aat	gtt	ttg	aga	ggg	ttc	agg	aaa	354	
Thr	Ile	Lys	Lys	Ser	Lys	Ala	Ile	Asn	Val	Leu	Arg	Gly	Phe	Arg	Lys		
				75					80					85			
gag	att	gga	agg	atg	ctg	aac	atc	ttg	aat	agg	aga	cgc	aga	tct	gca	402	
Glu	Ile	Gly	Arg	Met	Leu	Asn	Ile	Leu	Asn	Arg	Arg	Arg	Arg	Ser	Ala		
				90				95					100				
ggc	atg	atc	att	atg	ctg	att	cca	aca	gtg	atg	gcg	ttc	cat	tta	acc	450	
Gly	Met	Ile	Ile	Met	Leu	Ile	Pro	Thr	Val	Met	Ala	Phe	His	Leu	Thr		
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acg	cgt	gat	gga	gag	ccg	cgc	atg	att	gtg	ggg	aag	aat	gaa	aga	gga	498	
Thr	Arg	Asp	Gly	Glu	Pro	Arg	Met	Ile	Val	Gly	Lys	Asn	Glu	Arg	Gly		
	120					125					130						
aaa	tcc	cta	ctt	ttc	aag	aca	gcc	tct	gga	atc	aac	atg	tgc	aca	ctc	546	
Lys	Ser	Leu	Leu	Phe	Lys	Thr	Ala	Ser	Gly	Ile	Asn	Met	Cys	Thr	Leu		
135					140					145				150			
ata	gct	atg	gat	ctg	gga	gag	atg	tgt	gat	gac	acg	gtc	act	tac	aaa	594	
Ile	Ala	Met	Asp	Leu	Gly	Glu	Met	Cys	Asp	Thr	Val	Thr	Tyr	Lys			
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tgc	ccc	cac	att	acc	gaa	gtg	gag	cct	gaa	gac	att	gac	tgc	tgg	tgc	642	
Cys	Pro	His	Ile	Thr	Glu	Val	Glu	Pro	Glu	Asp	Ile	Asp	Cys	Trp	Cys		
				170				175					180				
aac	ctt	aca	tcg	aca	tgg	gtg	act	tat	gga	aca	tgc	aat	caa	gct	gga	690	
Asn	Leu	Thr	Ser	Thr	Trp	Val	Thr	Tyr	Gly	Thr	Cys	Asn	Gln	Ala	Gly		
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gag	cat	aga	cgc	gat	aag	aga	tca	gtg	gcg	tta	gct	ccc	cat	gtt	ggc	738	
Glu	His	Arg	Arg	Asp	Lys	Arg	Ser	Val	Ala	Leu	Ala	Pro	His	Val	Gly		
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Met	Gly	Leu	Asp	Thr	Arg	Thr	Gln	Thr	Trp	Met	Ser	Ala	Glu	Gly	Ala		
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Trp	Arg	Gln	Val	Glu	Lys	Val	Glu	Thr	Trp	Ala	Leu	Arg	His	Pro	Gly		
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ttt	acc	ata	cta	gcc	cta	ttt	ctt	gcc	cat	tac	ata	ggc	act	tcc	ttg	882	
Phe	Thr	Ile	Leu	Ala	Leu	Phe	Leu	Ala	His	Tyr	Ile	Gly	Thr	Ser	Leu		
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acc	cag	aaa	gtg	gtt	att	ttt	ata	cta	tta	atg	ctg	gtt	acc	cca	tcc	930	
Thr	Gln	Lys	Val	Val	Ile	Phe	Ile	Leu	Leu	Met	Leu	Val	Thr	Pro	Ser		
	265						270					275					

100

atg aca	atg aga	tgt gta	gga gta	gga aac	aga gat	ttt gtg	gaa ggc	978
Met Thr	Met Arg	Cys Val	Gly Val	Gly Asn	Arg Asp	Phe Val	Glu Gly	
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cta tcg	gga gct	acg tgg	gtt gac	gtg gtg	ctc gag	cac ggt	ggg tgt	1026
Leu Ser	Gly Ala	Thr Trp	Val Asp	Val Val	Leu Glu	His Gly	Gly Cys	
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gtg act	acc atg	gct aag	aac aag	ccc acg	ctg gac	ata gag	ctt cag	1074
Val Thr	Thr Met	Ala Lys	Asn Lys	Pro Thr	Leu Asp	Ile Glu	Leu Gln	
	315			320			325	
aag acc	gag gcc	acc caa	ctg gcg	acc cta	agg aag	cta tgc	att gag	1122
Lys Thr	Glu Ala	Thr Gln	Leu Ala	Thr Leu	Arg Lys	Leu Cys	Ile Glu	
	330			335			340	
gga aaa	att acc	aac ata	aca acc	gac tca	aga tgt	ccc acc	caa ggg	1170
Gly Lys	Ile Thr	Asn Ile	Thr Thr	Asp Ser	Arg Cys	Pro Thr	Gln Gly	
	345		350			355		
gaa gcg	att tta	cct gag	gag cag	gac cag	aac tac	gtg tgt	aag cat	1218
Glu Ala	Ile Leu	Pro Glu	Glu Gln	Asp Gln	Asn Tyr	Val Cys	Lys His	
360		365		370				
aca tac	gtg gac	aga ggc	tgg gga	aac ggt	tgt ggt	ttg ttt	ggc aag	1266
Thr Tyr	Val Asp	Arg Gly	Trp Gly	Asn Gly	Cys Gly	Leu Phe	Gly Lys	
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gga agc	ttg gtg	aca tgc	gcg aaa	ttt caa	tgt tta	gaa tca	ata gag	1314
Gly Ser	Leu Val	Thr Cys	Ala Lys	Phe Gln	Cys Leu	Glu Ser	Ile Glu	
	395			400			405	
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Gly Lys	Val Val	Gln His	Glu Asn	Leu Lys	Tyr Thr	Val Ile	Ile Thr	
	410			415			420	
gtg cac	aca gga	gac caa	cac cag	gtg gga	aat gaa	acg cag	gga gtc	1410
Val His	Thr Gly	Asp Gln	His Gln	Val Gly	Asn Glu	Thr Gln	Gly Val	
425			430				435	
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Thr Ala	Glu Ile	Thr Pro	Gln Ala	Ser Thr	Ala Glu	Ala Ile	Leu Pro	
440			445				450	
gaa tat	gga acc	ctc ggg	cta gaa	tgc tca	cca cgg	aca ggt	ttg gat	1506
Glu Tyr	Gly Thr	Leu Gly	Leu Glu	Cys Ser	Pro Arg	Thr Gly	Leu Asp	
455		460			465		470	
ttc aat	gaa atg	atc tca	ttg aca	atg aag	aac aaa	gca tgg	atg gta	1554
Phe Asn	Glu Met	Ile Ser	Leu Thr	Met Lys	Asn Lys	Ala Trp	Met Val	
	475			480			485	
cat aga	caa tgg	ttc ttt	gac tta	ccc cta	cca tgg	aca tca	gga gct	1602
His Arg	Gln Trp	Phe Phe	Asp Leu	Pro Leu	Pro Trp	Thr Ser	Gly Ala	
	490			495			500	

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gag gga gca atg cat aca gca ctg aca gga gct aca gag atc caa acc Glu Gly Ala Met His Thr Ala Leu Thr Gly Ala Thr Glu Ile Gln Thr 535 540 545 550	1746
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atg gac aaa ttg gaa ctc aag ggg atg agc tat gca atg tgc ttg agt Met Asp Lys Leu Glu Leu Lys Gly Met Ser Tyr Ala Met Cys Leu Ser 570 575 580	1842
agc ttt gtg ttg aag aaa gaa gtc tcc gaa acg cag cat ggg aca ata Ser Phe Val Leu Lys Lys Glu Val Ser Glu Thr Gln His Gly Thr Ile 585 590 595	1890
ctc att aag gtt gag tac aaa ggg gaa gat gca ccc tgc aag att cct Leu Ile Lys Val Glu Tyr Lys Gly Glu Asp Ala Pro Cys Lys Ile Pro 600 605 610	1938
ttc tcc acg gag gat gga caa gga aaa gct ctc aat ggc aga ctg atc Phe Ser Thr Glu Asp Gly Gln Gly Lys Ala Leu Asn Gly Arg Leu Ile 615 620 625 630	1986
aca gcc aat cca gtg gtg acc aag aag gag gag cct gtc aac att gag Thr Ala Asn Pro Val Val Thr Lys Lys Glu Glu Pro Val Asn Ile Glu 635 640 645	2034
gct gaa cct cct ttt gga gaa agt aac ata gta att gga att gga gac Ala Glu Pro Pro Phe Gly Glu Ser Asn Ile Val Ile Gly Ile Gly Asp 650 655 660	2082
aaa gcc ctg aaa atc aac tgg tac aag aag gga agc tcg att ggg aag Lys Ala Leu Lys Ile Asn Trp Tyr Lys Lys Gly Ser Ser Ile Gly Lys 665 670 675	2130
atg ttc gag gcc act gcc aga ggt gca agg cgc atg gcc atc ttg gga Met Phe Glu Ala Thr Ala Arg Gly Ala Arg Arg Met Ala Ile Leu Gly 680 685 690	2178
gac aca gcc tgg gac ttt gga tca gtg ggt ggt gtt ttg aat tca tta Asp Thr Ala Trp Asp Phe Gly Ser Val Gly Gly Val Leu Asn Ser Leu 695 700 705 710	2226

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ggg aaa atg gtc cac caa ata ttt ggg agt gct tac aca gcc cta ttt Gly Lys Met Val His Gln Ile Phe Gly Ser Ala Tyr Thr Ala Leu Phe 715 720 725	2274
ggt gga gtc tcc tgg atg atg aaa att gga ata ggt gtc ctc tta acc Gly Gly Val Ser Trp Met Met Lys Ile Gly Ile Gly Val Leu Leu Thr 730 735 740	2322
tgg ata ggg ttg aac tca aaa aat act tct atg tca ttt tca tgc atc Trp Ile Gly Leu Asn Ser Lys Asn Thr Ser Met Ser Phe Ser Cys Ile 745 750 755	2370
gcg gcc ggc att gtg aca ctg tat ttg gga gtc atg gtg cag gcc gat Ala Ala Gly Ile Val Thr Leu Tyr Leu Gly Val Met Val Gln Ala Asp 760 765 770	2418
agt ggt tgc gtt gtg agc tgg aaa aac aaa gaa ctg aaa tgt ggc agt Ser Gly Cys Val Val Ser Trp Lys Asn Lys Glu Leu Lys Cys Gly Ser 775 780 785 790	2466
ggg att ttc atc aca gac aac gtg cac aca tgg aca gaa caa tac aag Gly Ile Phe Ile Thr Asp Asn Val His Thr Trp Thr Glu Gln Tyr Lys 795 800 805	2514
ttc caa cca gaa tcc cct tca aaa cta gct tca gct atc cag aaa gcc Phe Gln Pro Glu Ser Pro Ser Lys Leu Ala Ser Ala Ile Gln Lys Ala 810 815 820	2562
cat gaa gag gac att tgt gga atc cgc tca gta aca aga ctg gag aat His Glu Glu Asp Ile Cys Gly Ile Arg Ser Val Thr Arg Leu Glu Asn 825 830 835	2610
ctg atg tgg aaa caa ata aca cca gaa ttg aat cac att cta tca gaa Leu Met Trp Lys Gln Ile Thr Pro Glu Leu Asn His Ile Leu Ser Glu 840 845 850	2658
aat gag gtg aag tta act att atg aca gga gac atc aaa gga atc atg Asn Glu Val Lys Leu Thr Ile Met Thr Gly Asp Ile Lys Gly Ile Met 855 860 865 870	2706
cag gca gga aaa cga tct ctg cgg cct cag ccc act gag ctg aag tat Gln Ala Gly Lys Arg Ser Leu Arg Pro Gln Pro Thr Glu Leu Lys Tyr 875 880 885	2754
tca tgg aaa aca tgg ggc aaa gca aaa atg ctc tct aca gag tct cat Ser Trp Lys Thr Trp Gly Lys Ala Lys Met Leu Ser Thr Glu Ser His 890 895 900	2802
aac cag acc ttt ctc att gat ggc ccc gaa aca gca gaa tgc ccc aac Asn Gln Thr Phe Leu Ile Asp Gly Pro Glu Thr Ala Glu Cys Pro Asn 905 910 915	2850
aca aat aga gct tgg aat tcg ttg gaa gtt gaa gac tat ggc ttt gga Thr Asn Arg Ala Trp Asn Ser Leu Glu Val Glu Asp Tyr Gly Phe Gly 920 925 930	2898

gta ttc acc acc aat ata tgg cta aaa ttg aaa gaa aaa cag gat gta Val Phe Thr Thr Asn Ile Trp Leu Lys Leu Lys Glu Lys Gln Asp Val 935 940 945 950	2946
ttc tgc gac tca aaa ctc atg tca gcg gcc ata aaa gac aac aga gcc Phe Cys Asp Ser Lys Leu Met Ser Ala Ala Ile Lys Asp Asn Arg Ala 955 960 965	2994
gtc cat gcc gat atg ggt tat tgg ata gaa agt gca ctc aat gac aca Val His Ala Asp Met Gly Tyr Trp Ile Glu Ser Ala Leu Asn Asp Thr 970 975 980	3042
tgg aag ata gag aaa gcc tct ttc att gaa gtt aaa aac tgc cac tgg Trp Lys Ile Glu Lys Ala Ser Phe Ile Glu Val Lys Asn Cys His Trp 985 990 995	3090
cca aaa tca cac acc ctc tgg agc aat gga gtg cta gaa agt gag atg Pro Lys Ser His Thr Leu Trp Ser Asn Gly Val Leu Glu Ser Glu Met 1000 1005 1010	3138
ata att cca aag aat ctc gct gga cca gtg tct caa cac aac tat aga Ile Ile Pro Lys Asn Leu Ala Gly Pro Val Ser Gln His Asn Tyr Arg 1015 1020 1025 1030	3186
cca ggc tac cat aca caa ata aca gga cca tgg cat cta ggt aag ctt Pro Gly Tyr His Thr Gln Ile Thr Gly Pro Trp His Leu Gly Lys Leu 1035 1040 1045	3234
gag atg gac ttt gat ttc tgt gat gga aca aca gtg gta gtg act gag Glu Met Asp Phe Asp Phe Cys Asp Gly Thr Thr Val Val Val Thr Glu 1050 1055 1060	3282
gac tgc gga aat aga gga ccc tct ttg aga aca acc act gcc tct gga Asp Cys Gly Asn Arg Gly Pro Ser Leu Arg Thr Thr Ala Ser Gly 1065 1070 1075	3330
aaa ctc ata aca gaa tgg tgc tgc cga tct tgc aca tta cca ccg cta Lys Leu Ile Thr Glu Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro Leu 1080 1085 1090	3378
aga tac aga ggt gag gat ggg tgc tgg tac ggg atg gaa atc aga cca Arg Tyr Arg Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro 1095 1100 1105 1110	3426
ttg aag gag aaa gaa gag aat ttg gtc aac tcc ttg gtc aca gct gga Leu Lys Glu Lys Glu Glu Asn Leu Val Asn Ser Leu Val Thr Ala Gly 1115 1120 1125	3474
cat ggg cag gtc gac aac ttt tca cta gga gtc ttg gga atg gca ttg His Gly Gln Val Asp Asn Phe Ser Leu Gly Val Leu Gly Met Ala Leu 1130 1135 1140	3522

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ttc ctg gag gaa atg ctt agg acc cga gta gga acg aaa cat gca ata Phe Leu Glu Glu Met Leu Arg Thr Arg Val Gly Thr Lys His Ala Ile 1145 1150 1155	3570
cta cta gtt gca gtt tct ttt gtg aca ttg atc aca ggg aac atg tcc Leu Leu Val Ala Val Ser Phe Val Thr Leu Ile Thr Gly Asn Met Ser 1160 1165 1170	3618
ttt aga gac ctg gga aga gtg atg gtt atg gta ggc gcc act atg acg Phe Arg Asp Leu Gly Arg Val Met Val Met Val Gly Ala Thr Met Thr 1175 1180 1185 1190	3666
gat gac ata ggt atg ggc gtg act tat ctt gcc cta cta gca gcc ttc Asp Asp Ile Gly Met Gly Val Thr Tyr Leu Ala Leu Leu Ala Ala Phe 1195 1200 1205	3714
aaa gtc aga cca act ttt gca gct gga cta ctc ttg aga aag ctg acc Lys Val Arg Pro Thr Phe Ala Ala Gly Leu Leu Leu Arg Lys Leu Thr 1210 1215 1220	3762
tcc aag gaa ttg atg atg act act ata gga att gta ctc ctc tcc cag Ser Lys Glu Leu Met Met Thr Thr Ile Gly Ile Val Leu Leu Ser Gln 1225 1230 1235	3810
agc acc ata cca gag acc att ctt gag ttg act gat gcg tta gcc tta Ser Thr Ile Pro Glu Thr Ile Leu Glu Leu Thr Asp Ala Leu Ala Leu 1240 1245 1250	3858
ggc atg atg gtc ctc aaa atg gtg aga aat atg gaa aag tat caa ttg Gly Met Met Val Leu Lys Met Val Arg Asn Met Glu Lys Tyr Gln Leu 1255 1260 1265 1270	3906
gca gtg act atc atg gct atc ttg tgc gtc cca aac gca gtg ata tta Ala Val Thr Ile Met Ala Ile Leu Cys Val Pro Asn Ala Val Ile Leu 1275 1280 1285	3954
caa aac gca tgg aaa gtg agt tgc aca ata ttg gca gtg gtg tcc gtt Gln Asn Ala Trp Lys Val Ser Cys Thr Ile Leu Ala Val Ser Val 1290 1295 1300	4002
tcc cca ctg ttc tta aca tcc tca cag caa aaa aca gat tgg ata cca Ser Pro Leu Phe Leu Thr Ser Ser Gln Gln Lys Thr Asp Trp Ile Pro 1305 1310 1315	4050
tta gca ttg acg atc aaa ggt ctc aat cca aca gct att ttt cta aca Leu Ala Leu Thr Ile Lys Gly Leu Asn Pro Thr Ala Ile Phe Leu Thr 1320 1325 1330	4098
acc ctc tca aga acc agc aag aaa agg agc tgg cca tta aat gag gct Thr Leu Ser Arg Thr Ser Lys Lys Arg Ser Trp Pro Leu Asn Glu Ala 1335 1340 1345 1350	4146
atc atg gca gtc ggg atg gtg agc att tta gcc agt tct ctc cta aaa Ile Met Ala Val Gly Met Val Ser Ile Leu Ala Ser Ser Leu Leu Lys 1355 1360 1365	4194

aat gat att ccc atg aca gga cca tta gtg gct gga ggg ctc ctc act	4242
Asn Asp Ile Pro Met Thr Gly Pro Leu Val Ala Gly Gly Leu Leu Thr	
1370 1375 1380	
gtg tgc tac gtg ctc act gga cga tgc gcc gat ttg gaa ctg gag aga	4290
Val Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu Leu Glu Arg	
1385 1390 1395	
gca gcc gat gtc aaa tgg gaa gac cag gca gag ata tca gga agc agt	4338
Ala Ala Asp Val Lys Trp Glu Asp Gln Ala Glu Ile Ser Gly Ser Ser	
1400 1405 1410	
cca atc ctg tca ata aca ata tca gaa gat ggt agc atg tgc ata aaa	4386
Pro Ile Leu Ser Ile Thr Ile Ser Glu Asp Gly Ser Met Ser Ile Lys	
1415 1420 1425 1430	
aat gaa gag gaa gaa caa aca ctg acc ata ctc att aga aca gga ttg	4434
Asn Glu Glu Glu Glu Gln Thr Leu Thr Ile Leu Ile Arg Thr Gly Leu	
1435 1440 1445	
ctg gtg atc tca gga ctt ttt cct gta tca ata cca atc acg gca gca	4482
Leu Val Ile Ser Gly Leu Phe Pro Val Ser Ile Pro Ile Thr Ala Ala	
1450 1455 1460	
gca tgg tac ctg tgg gaa gtg aag aaa caa cgg gcc gga gta ttg tgg	4530
Ala Trp Tyr Leu Trp Glu Val Lys Lys Gln Arg Ala Gly Val Leu Trp	
1465 1470 1475	
gat gtt cct tca ccc cca ccc atg gga aag gct gaa ctg gaa gat gga	4578
Asp Val Pro Ser Pro Pro Pro Met Gly Lys Ala Glu Leu Glu Asp Gly	
1480 1485 1490	
gcc tat aga att aag caa aaa ggg att ctt gga tat tcc cag atc gga	4626
Ala Tyr Arg Ile Lys Gln Lys Gly Ile Leu Gly Tyr Ser Gln Ile Gly	
1495 1500 1505 1510	
gcc gga gtt tac aaa gaa gga aca ttc cat aca atg tgg cat gtc aca	4674
Ala Gly Val Tyr Lys Glu Gly Thr Phe His Thr Met Trp His Val Thr	
1515 1520 1525	
cgt gcc gct gtt cta atg cat aaa gga aag agg att gaa cca tca tgg	4722
Arg Gly Ala Val Leu Met His Lys Gly Lys Arg Ile Glu Pro Ser Trp	
1530 1535 1540	
gcg gac gtc aag aaa gac cta ata tca tat gga gga gcc tgg aag tta	4770
Ala Asp Val Lys Lys Asp Leu Ile Ser Tyr Gly Gly Gly Trp Lys Leu	
1545 1550 1555	
gaa gga gaa tgg aag gaa gga gaa gaa gtc cag gta ttg gca ctg gag	4818
Glu Gly Glu Trp Lys Glu Gly Glu Glu Val Gln Val Leu Ala Leu Glu	
1560 1565 1570	

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cct gga aaa aat cca aga gcc gtc caa acg aaa cct ggt ctt ttc aaa Pro Gly Lys Asn Pro Arg Ala Val Gln Thr Lys Pro Gly Leu Phe Lys 1575 1580 1585 1590	4866
acc aac gcc gga aca ata ggt gct gta tct ctg gac ttt tct cct gga Thr Asn Ala Gly Thr Ile Gly Ala Val Ser Leu Asp Phe Ser Pro Gly 1595 1600 1605	4914
acg tca gga tct cca att atc gac aaa aaa gga aaa gtt gtg ggt ctt Thr Ser Gly Ser Pro Ile Ile Asp Lys Lys Gly Lys Val Val Gly Leu 1610 1615 1620	4962
tat ggt aat ggt gtt gtt aca agg agt gga gca tat gtg agt gct ata Tyr Gly Asn Gly Val Val Thr Arg Ser Gly Ala Tyr Val Ser Ala Ile 1625 1630 1635	5010
gcc cag act gaa aaa agc att gaa gac aac cca gag atc gaa gat gac Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile Glu Asp Asp 1640 1645 1650	5058
att ttc cga aag aga aga ctg acc atc atg gac ctc cac cca gga gcg Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu His Pro Gly Ala 1655 1660 1665 1670	5106
gga aag acg aag aga tac ctt ccg gcc ata gtc aga gaa gct ata aaa Gly Lys Thr Lys Arg Tyr Leu Pro Ala Ile Val Arg Glu Ala Ile Lys 1675 1680 1685	5154
egg ggt ttg aga aca tta atc ttg gcc ccc act aga gtt gtg gca gct Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro Thr Arg Val Val Ala Ala 1690 1695 1700	5202
gaa atg gag gaa gcc ctt aga gga ctt cca ata aga tac cag acc cca Glu Met Glu Glu Ala Leu Arg Gly Leu Pro Ile Arg Tyr Gln Thr Pro 1705 1710 1715	5250
gcc atc aga gct gtg cac acc ggg cgg gag att gtg gac cta atg tgt Ala Ile Arg Ala Val His Thr Gly Arg Glu Ile Val Asp Leu Met Cys 1720 1725 1730	5298
cat gcc aca ttt acc atg agg ctg cta tca cca gtt aga gtg cca aac His Ala Thr Phe Thr Met Arg Leu Leu Ser Pro Val Arg Val Pro Asn 1735 1740 1745 1750	5346
tac aac ctg att atc atg gac gaa gcc cat ttc aca gac cca gca agt Tyr Asn Leu Ile Ile Met Asp Glu Ala His Phe Thr Asp Pro Ala Ser 1755 1760 1765	5394
ata gca gct aga gga tac atc tca act cga gtg gag atg ggt gag gca Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Glu Met Gly Glu Ala 1770 1775 1780	5442
gct ggg att ttt atg aca gcc act ccc ccg gga agc aga gac cca ttt Ala Gly Ile Phe Met Thr Ala Thr Pro Pro Gly Ser Arg Asp Pro Phe 1785 1790 1795	5490

cct cag agc aat gca cca atc ata gat gaa gaa aga gaa atc cct gaa Pro Gln Ser Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu Ile Pro Glu 1800 1805 1810	5538
cgc tcg tgg aat tcc gga cat gaa tgg gtc acg gat ttt aaa ggg aag Arg Ser Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe Lys Gly Lys 1815 1820 1825 1830	5586
act gtt tgg ttc gtt cca agt ata aaa gca gga aat gat ata gca gct Thr Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile Ala Ala 1835 1840 1845	5634
tgc ctg agg aaa aat gga aag aaa gtg ata caa ctc agt agg aag acc Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg Lys Thr 1850 1855 1860	5682
ttt gat tct gag tat gtc aag act aga acc aat gat tgg gac ttc gtg Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp Phe Val 1865 1870 1875	5730
gtt aca act gac att tca gaa atg ggt gcc aat ttc aag gct gag agg Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys Ala Glu Arg 1880 1885 1890	5778
gtt ata gac ccc aga cgc tgc atg aaa cca gtc ata cta aca gat ggt Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile Leu Thr Asp Gly 1895 1900 1905 1910	5826
gaa gag cgg gtg att ctg gca gga cct atg cca gtg acc cac tct agt Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr His Ser Ser 1915 1920 1925	5874
gca gca caa aga aga ggg aga ata gga aga aat cca aaa aat gag aat Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro Lys Asn Glu Asn 1930 1935 1940	5922
gac cag tac ata tac atg ggg gaa cct ctg gaa aat gat gaa gac tgt Asp Gln Tyr Ile Tyr Met Gly Glu Pro Leu Glu Asn Asp Glu Asp Cys 1945 1950 1955	5970
gca cac tgg aaa gaa gct aaa atg ctc cta gat aac atc aac acg cca Ala His Trp Lys Glu Ala Lys Met Leu Leu Asp Asn Ile Asn Thr Pro 1960 1965 1970	6018
gaa gga atc att cct agc atg ttc gaa cca gag cgt gaa aag gtg gat Glu Gly Ile Ile Pro Ser Met Phe Glu Pro Glu Arg Glu Lys Val Asp 1975 1980 1985 1990	6066
gcc att gat ggc gaa tac cgc ttg aga gga gaa gca agg aaa acc ttt Ala Ile Asp Gly Glu Tyr Arg Leu Arg Gly Glu Ala Arg Lys Thr Phe 1995 2000 2005	6114

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gta gac tta atg aga aga gga gac cta cca gtc tgg ttg gcc tac aga Val Asp Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ala Tyr Arg 2010 2015 2020	6162
gtg gca gct gaa ggc atc aac tac gca gac aga agg tgg tgt ttt gat Val Ala Ala Glu Gly Ile Asn Tyr Ala Asp Arg Arg Trp Cys Phe Asp 2025 2030 2035	6210
gga gtc aag aac aac caa atc cta gaa gaa aac gtg gaa gtt gaa atc Gly Val Lys Asn Asn Gln Ile Leu Glu Glu Asn Val Glu Val Glu Ile 2040 2045 2050	6258
tgg aca aaa gaa ggg gaa agg aag aaa ttg aaa ccc aga tgg ttg gat Trp Thr Lys Glu Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp Leu Asp 2055 2060 2065 2070	6306
gct agg atc tat tct gac cca ctg gcg cta aaa gaa ttt aag gaa ttt Ala Arg Ile Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys Glu Phe 2075 2080 2085	6354
gca gcc gga aga aag tct ctg acc ctg aac cta atc aca gaa atg ggt Ala Ala Gly Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu Met Gly 2090 2095 2100	6402
agg ctc cca acc ttc atg act cag aag gca aga gac gca ctg gac aac Arg Leu Pro Thr Phe Met Thr Gln Lys Ala Arg Asp Ala Leu Asp Asn 2105 2110 2115	6450
tta gca gtg ctg cac acg gct gag gca ggt gga agg gcg tac aac cat Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala Tyr Asn His 2120 2125 2130	6498
gct ctc agt gaa ctg ccg gag acc ctg gag aca ttg ctt tta ctg aca Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu Leu Leu Thr 2135 2140 2145 2150	6546
ctt ctg gct aca gtc acg gga ggg atc ttt tta ttc ttg atg agc gca Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu Phe Leu Met Ser Ala 2155 2160 2165	6594
agg ggc ata ggg aag atg acc ctg gga atg tgc tgc ata atc acg gct Arg Gly Ile Gly Lys Met Thr Leu Gly Met Cys Cys Ile Ile Thr Ala 2170 2175 2180	6642
agc atc ctc cta tgg tac gca caa ata cag cca cac tgg ata gca gct Ser Ile Leu Leu Trp Tyr Ala Gln Ile Gln Pro His Trp Ile Met Ala 2185 2190 2195	6690
tca ata ata ctg gag ttt ttt ctc ata gtt ttg ctt att cca gaa cct Ser Ile Ile Leu Glu Phe Phe Leu Ile Val Leu Leu Ile Pro Glu Pro 2200 2205 2210	6738
gaa aaa cag aga aca ccc caa gac aac caa ctg acc tac gtt gtc ata Glu Lys Gln Arg Thr Pro Gln Asp Asn Gln Leu Thr Tyr Val Val Ile 2215 2220 2225 2230	6786

gcc atc ctc aca gtg gtg gcc gca acc atg gca aac gag atg ggt ttc Ala Ile Leu Thr Val Val Ala Ala Thr Met Ala Asn Glu Met Gly Phe 2235 2240 2245	6834
cta gaa aaa acg aag aaa gat ctc gga ttg gga agc att gca acc cag Leu Glu Lys Thr Lys Lys Asp Leu Gly Leu Gly Ser Ile Ala Thr Gln 2250 2255 2260	6882
caa ccc gag agc aac atc ctg gac ata gat cta cgt cct gca tca gca Gln Pro Glu Ser Asn Ile Leu Asp Ile Asp Leu Arg Pro Ala Ser Ala 2265 2270 2275	6930
tgg acg ctg tat gcc gtg gcc aca aca ttt gtt aca cca atg ttg aga Trp Thr Leu Tyr Ala Val Ala Thr Thr Phe Val Thr Pro Met Leu Arg 2280 2285 2290	6978
cat agc att gaa aat tcc tca gtg aat gtg tcc cta aca gct ata gcc His Ser Ile Glu Asn Ser Ser Val Asn Val Ser Leu Thr Ala Ile Ala 2295 2300 2305 2310	7026
aac caa gcc aca gtg tta atg ggt ctc ggg aaa gga tgg cca ttg tca Asn Gln Ala Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro Leu Ser 2315 2320 2325	7074
aag atg gac atc gga gtt ccc ctt ctc gcc att gga tgc tac tca caa Lys Met Asp Ile Gly Val Pro Leu Leu Ala Ile Gly Cys Tyr Ser Gln 2330 2335 2340	7122
gtc aac ccc ata act ctc aca gca gct ctt ttc tta ttg gta gca cat Val Asn Pro Ile Thr Leu Thr Ala Ala Leu Phe Leu Leu Val Ala His 2345 2350 2355	7170
tat gcc atc ata ggg cca gga ctc caa gca aaa gca acc aga gaa gct Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg Glu Ala 2360 2365 2370	7218
cag aaa aga gca gcg gcg ggc atc atg aaa aac cca act gtc gat gga Gln Lys Arg Ala Ala Ala Gly Ile Met Lys Asn Pro Thr Val Asp Gly 2375 2380 2385 2390	7266
ata aca gtg att gac cta gat cca ata cct tat gat cca aag ttt gaa Ile Thr Val Ile Asp Leu Asp Pro Ile Pro Tyr Asp Pro Lys Phe Glu 2395 2400 2405	7314
aag cag ttg gga caa gta atg ctc cta gtc ctc tgc gtg act caa gta Lys Gln Leu Gly Gln Val Met Leu Leu Val Leu Cys Val Thr Gln Val 2410 2415 2420	7362
ttg atg atg agg act aca tgg gct ctg tgt gag gct tta acc tta gct Leu Met Met Arg Thr Thr Trp Ala Leu Cys Glu Ala Leu Thr Leu Ala 2425 2430 2435	7410

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acc ggg ccc atc tcc aca ttg tgg gaa gga aat cca ggg agg ttt tgg Thr Gly Pro Ile Ser Thr Leu Trp Glu Gly Asn Pro Gly Arg Phe Trp 2440 2445 2450	7458
aac act acc att gcg gtg tca atg gct aac att ttt aga ggg agt tac Asn Thr Thr Ile Ala Val Ser Met Ala Asn Ile Phe Arg Gly Ser Tyr 2455 2460 2465 2470	7506
ttg gcc gga gct gga ctt ctc ttt tct att atg aag aac aca acc aac Leu Ala Gly Ala Gly Leu Leu Phe Ser Ile Met Lys Asn Thr Thr Asn 2475 2480 2485	7554
aca aga agg gga act ggc aac ata gga gag acg ctt gga gag aaa tgg Thr Arg Arg Gly Thr Gly Asn Ile Gly Glu Thr Leu Gly Glu Lys Trp 2490 2495 2500	7602
aaa agc cga ttg aac gca ttg gga aaa agt gaa ttc cag atc tac aag Lys Ser Arg Leu Asn Ala Leu Gly Lys Ser Glu Phe Gln Ile Tyr Lys 2505 2510 2515	7650
aaa agt gga atc cag gaa gtg gat aga acc tta gca aaa gaa ggc att Lys Ser Gly Ile Gln Glu Val Asp Arg Thr Leu Ala Lys Glu Gly Ile 2520 2525 2530	7698
aaa aga gga gaa acg gac cat cac gct gtg tgg cga ggc tca gca aaa Lys Arg Gly Glu Thr Asp His His Ala Val Ser Arg Gly Ser Ala Lys 2535 2540 2545 2550	7746
ctg aga tgg ttc gtt gag aga aac atg gtc aca cca gaa ggg aaa gta Leu Arg Trp Phe Val Glu Arg Asn Met Val Thr Pro Glu Gly Lys Val 2555 2560 2565	7794
gtg gac ctc ggt tgt ggc aga gga ggc tgg tca tac tat tgt gga gga Val Asp Leu Gly Cys Gly Arg Gly Gly Trp Ser Tyr Tyr Cys Gly Gly 2570 2575 2580	7842
cta aag aat gta aga gaa gtc aaa ggc cta aca aaa gga gga cca gga Leu Lys Asn Val Arg Glu Val Lys Gly Leu Thr Lys Gly Gly Pro Gly 2585 2590 2595	7890
cac gaa gaa ccc atc ccc atg tca aca tat ggg tgg aat cta gtg cgt His Glu Glu Pro Ile Pro Met Ser Thr Tyr Gly Trp Asn Leu Val Arg 2600 2605 2610	7938
ctt caa agt gga gtt gac gtt ttc ttc atc ccg cca gaa aag tgt gac Leu Gln Ser Gly Val Asp Val Phe Phe Ile Pro Glu Lys Cys Asp 2615 2620 2625 2630	7986
aca tta ttg tgt gac ata ggg gag tca tca cca aat ccc aca gtg gaa Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro Thr Val Glu 2635 2640 2645	8034
gca gga cga aca ctc aga gtc ctt aac tta gta gaa aat tgg ttg aac Ala Gly Arg Thr Leu Arg Val Leu Asn Leu Val Glu Asn Trp Leu Asn 2650 2655 2660	8082

111

aac aac act caa ttt tgc ata aag gtt ctc aac cca tat atg ccc tca Asn Asn Thr Gln Phe Cys Ile Lys Val Leu Asn Pro Tyr Met Pro Ser 2665 2670 2675	8130
gtc ata gaa aaa atg gaa gca cta caa agg aaa tat gga gga gcc tta Val Ile Glu Lys Met Glu Ala Leu Gln Arg Lys Tyr Gly Gly Ala Leu 2680 2685 2690	8178
gtg agg aat cca ctc tca cga aac tcc aca cat gag atg tac tgg gta Val Arg Asn Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr Trp Val 2695 2700 2705 2710	8226
tcc aat gct tcc ggg aac ata gtg tca tca gtg aac atg att tca agg Ser Asn Ala Ser Gly Asn Ile Val Ser Ser Val Asn Met Ile Ser Arg 2715 2720 2725	8274
atg ttg atc aac aga ttt aca atg aga tac aag aaa gcc act tac gag Met Leu Ile Asn Arg Phe Thr Met Arg Tyr Lys Lys Ala Thr Tyr Glu 2730 2735 2740	8322
ccg gat gtt gac ctc gga agc gga acc cgt aac atc ggg att gaa agt Pro Asp Val Asp Leu Gly Ser Gly Thr Arg Asn Ile Gly Ile Glu Ser 2745 2750 2755	8370
gag ata cca aac cta gat ata att ggg aaa aga ata gaa aaa ata aag Glu Ile Pro Asn Leu Asp Ile Ile Gly Lys Arg Ile Glu Lys Ile Lys 2760 2765 2770	8418
caa gag cat gaa aca tca tgg cac tat gac caa gac cac cca tac aaa Gln Glu His Glu Thr Ser Trp His Tyr Asp Gln Asp His Pro Tyr Lys 2775 2780 2785 2790	8466
acg tgg gca tac cat ggt agc tat gaa aca aaa cag act gga tca gca Thr Trp Ala Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly Ser Ala 2795 2800 2805	8514
tca tcc atg gtc aac gga gtg gtc agg ctg ctg aca aaa cct tgg gac Ser Ser Met Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro Trp Asp 2810 2815 2820	8562
gtc gtc ccc atg gtg aca cag atg gca atg aca gac acg act cca ttt Val Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Pro Phe 2825 2830 2835	8610
gga caa cag cgc gtt ttt aaa gag aaa gtg gac acg aga acc caa gaa Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr Gln Glu 2840 2845 2850	8658
ccg aaa gaa ggc acg aag aaa cta atg aaa ata aca gca gag tgg ctt Pro Lys Glu Gly Thr Lys Lys Leu Met Lys Ile Thr Ala Glu Trp Leu 2855 2860 2865 2870	8706

112

tgg aaa gaa tta ggg aag aaa aag aca ccc agg atg tgc acc aga gaa Trp Lys Glu Leu Gly Lys Lys Lys Thr Pro Arg Met Cys Thr Arg Glu	8754
2875 2880 2885	
gaa ttc aca aga aag gtg aga agc aat gca gcc ttg ggg gcc ata ttc Glu Phe Thr Arg Lys Val Arg Ser Asn Ala Ala Leu Gly Ala Ile Phe	8802
2890 2895 2900	
act gat gag aac aag tgg aag tcg gca cgt gag gct gtt gaa gat agt Thr Asp Glu Asn Lys Trp Lys Ser Ala Arg Glu Ala Val Glu Asp Ser	8850
2905 2910 2915	
agg ttt tgg gag ctg gtt gac aag gaa agg aat ctc cat ctt gaa gga Arg Phe Trp Glu Leu Val Asp Lys Glu Arg Asn Leu His Leu Glu Gly	8898
2920 2925 2930	
aag tgt gaa aca tgt gtg tac aac atg atg gga aaa aga gag aag aag Lys Cys Glu Thr Cys Val Tyr Asn Met Met Gly Lys Arg Glu Lys Lys	8946
2935 2940 2945 2950	
cta ggg gaa ttc ggc aag gca aaa ggc agc aga gcc ata tgg tac atg Leu Gly Glu Phe Gly Lys Ala Lys Gly Ser Arg Ala Ile Trp Tyr Met	8994
2955 2960 2965	
tgg ctt gga gca cgc ttc tta gag ttt gaa gcc cta gga ttc tta aat Trp Leu Gly Ala Arg Phe Leu Glu Phe Glu Ala Leu Gly Phe Leu Asn	9042
2970 2975 2980	
gaa gat cac tgg ttc tcc aga gag aac tcc ctg agt gga gtg gaa gga Glu Asp His Trp Phe Ser Arg Glu Asn Ser Leu Ser Gly Val Glu Gly	9090
2985 2990 2995	
gaa ggg ctg cac aag cta ggt tac att cta aga gac gtg agc aag aaa Glu Gly Leu His Lys Leu Gly Tyr Ile Leu Arg Asp Val Ser Lys Lys	9138
3000 3005 3010	
gag gga gga gca atg tat gcc gat gac acc gca gga tgg gat aca aga Glu Gly Gly Ala Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp Thr Arg	9186
3015 3020 3025 3030	
atc aca cta gaa gac cta aaa aat gaa gaa atg gta aca aac cac atg Ile Thr Leu Glu Asp Leu Lys Asn Glu Glu Met Val Thr Asn His Met	9234
3035 3040 3045	
gaa gga gaa cac aag aaa cta gcc gag gcc att ttc aaa cta acg tac Glu Gly Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu Thr Tyr	9282
3050 3055 3060	
caa aac aag gtg gtg cgt gtg caa aga cca aca cca aga ggc aca gta Gln Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly Thr Val	9330
3065 3070 3075	
atg gac atc ata tcg aga aga gac caa aga ggt agt gga caa gtt ggc Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly Gln Val Gly	9378
3080 3085 3090	

113

acc tat gga ctc aat act ttc acc aat atg gaa gcc caa cta atc aga Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu Ile Arg 3095 3100 3105 3110	9426
cag atg gag gga gaa gga gtc ttt aaa agc att cag cac cta aca atc Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile Gln His Leu Thr Ile 3115 3120 3125	9474
aca gaa gaa atc gct gtg caa aac tgg tta gca aga gtg ggg cgc gaa Thr Glu Glu Ile Ala Val Gln Asn Trp Leu Ala Arg Val Gly Arg Glu 3130 3135 3140	9522
agg tta tca aga atg gcc atc agt gga gat gat tgt gtt gtg aaa cct Arg Leu Ser Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val Lys Pro 3145 3150 3155	9570
tta gat gac agg ttc gca agc gct tta aca gct cta aat gac atg gga Leu Asp Asp Arg Phe Ala Ser Ala Leu Thr Ala Leu Asn Asp Met Gly 3160 3165 3170	9618
aag att agg aaa gac ata caa caa tgg gaa cct tca aga gga tgg aat Lys Ile Arg Lys Asp Ile Gln Gln Trp Glu Pro Ser Arg Gly Trp Asn 3175 3180 3185 3190	9666
gat tgg aca caa gtg ccc ttc tgt tca cac cat ttc cat gag tta atc Asp Trp Thr Gln Val Pro Phe Cys Ser His His Phe His Glu Leu Ile 3195 3200 3205	9714
atg aaa gac ggt cgc gta ctc gtt gtt cca tgt aga aac caa gat gaa Met Lys Asp Gly Arg Val Leu Val Val Pro Cys Arg Asn Gln Asp Glu 3210 3215 3220	9762
ctg att ggc aga gcc cga atc tcc caa gga gca ggg tgg tct ttg cgg Leu Ile Gly Arg Ala Arg Ile Ser Gln Gly Ala Gly Trp Ser Leu Arg 3225 3230 3235	9810
gag acg gcc tgt ttg ggg aag tct tac gcc caa atg tgg agc ttg atg Glu Thr Ala Cys Leu Gly Lys Ser Tyr Ala Gln Met Trp Ser Leu Met 3240 3245 3250	9858
tac ttc cac aga cgc gac ctc agg ctg gcg gca aat gct att tgc tcg Tyr Phe His Arg Arg Asp Leu Arg Leu Ala Ala Asn Ala Ile Cys Ser 3255 3260 3265 3270	9906
gca gta cca tca cat tgg gtt cca aca agt cga aca acc tgg tcc ata Ala Val Pro Ser His Trp Val Pro Thr Ser Arg Thr Thr Trp Ser Ile 3275 3280 3285	9954
cat gct aaa cat gaa tgg atg aca acg gaa gac atg ctg aca gtc tgg His Ala Lys His Glu Trp Met Thr Thr Glu Asp Met Leu Thr Val Trp 3290 3295 3300	10002

114

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aac agg gtg tgg att caa gaa aac cca tgg atg gaa gac aaa act cca      10050
Asn Arg Val Trp Ile Gln Glu Asn Pro Trp Met Glu Asp Lys Thr Pro
      3305              3310              3315

gtg gaa tca tgg gag gaa atc cca tac ttg ggg aaa aga gaa gac caa      10098
Val Glu Ser Trp Glu Glu Ile Pro Tyr Leu Gly Lys Arg Glu Asp Gln
      3320              3325              3330

tgg tgc ggc tca ttg att ggg tta aca agc agg gcc acc tgg gca aag      10146
Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala Thr Trp Ala Lys
      3335              3340              3345              3350

aac atc caa gca gca ata aat caa gtt aga tcc ctt ata ggc aat gaa      10194
Asn Ile Gln Ala Ala Ile Asn Gln Val Arg Ser Leu Ile Gly Asn Glu
      3355              3360              3365

gaa tac aca gat tac atg cca tcc atg aaa aga ttc aga aga gaa gag      10242
Glu Tyr Thr Asp Tyr Met Pro Ser Met Lys Arg Phe Arg Arg Glu Glu
      3370              3375              3380

gaa gaa gca gga gtt ctg tgg tag aaagcaaaac taacatgaaa caaggctaga      10296
Glu Glu Ala Gly Val Leu Trp *
      3385

agtcaggctcg gattaagcca tagtacggaa aaaactatgc tacctgtgag ccccgctcaa      10356
ggacgttaaa agaagtcagg ccatcataaa tgccatagct tgagtaaact atgcagcctg      10416
tagctccacc tgagaagggt taaaaaatcc gggaggccac aaaccatgga agctgtacgc      10476
atggcgtagt ggactagcgg ttagaggaga cccctccctt acaaatcgca gcaacaatgg      10536
gggccaagg cgagatgaag ctgtagtctc gctggaagga ctagggtta gaggagacc      10596
ccccaaaaca aaaaacagca tattgacgct gggaaagacc agagatcctg ctgtctctc      10656
agcatcattc caggcacaga acgccagaaa atggaatggt gctgttgaat caacaggttc      10716
t                                                                 10717

<210> 10
<211> 3389
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/Note =
      synthetic construct

<400> 10
Met Asn Asn Gln Arg Lys Lys Ala Lys Asn Thr Pro Phe Asn Met Leu
 1              5              10              15
Lys Arg Glu Arg Asn Arg Val Ser Thr Val Gln Gln Leu Thr Lys Arg
      20              25              30
Phe Ser Leu Gly Met Leu Gln Gly Arg Gly Pro Leu Lys Leu Phe Met
      35              40              45
Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly
      50              55              60
Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val
      65              70              75              80

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Leu	Arg	Gly	Phe	Arg	Lys	Glu	Ile	Gly	Arg	Met	Leu	Asn	Ile	Leu	Asn	
			85						90					95		
Arg	Arg	Arg	Arg	Ser	Ala	Gly	Met	Ile	Ile	Met	Leu	Ile	Pro	Thr	Val	
			100					105					110			
Met	Ala	Phe	His	Leu	Thr	Thr	Arg	Asp	Gly	Glu	Pro	Arg	Met	Ile	Val	
		115					120					125				
Gly	Lys	Asn	Glu	Arg	Gly	Lys	Ser	Leu	Leu	Phe	Lys	Thr	Ala	Ser	Gly	
	130					135					140					
Ile	Asn	Met	Cys	Thr	Leu	Ile	Ala	Met	Asp	Leu	Gly	Glu	Met	Cys	Asp	
	145			150					155					160		
Asp	Thr	Val	Thr	Tyr	Lys	Cys	Pro	His	Ile	Thr	Glu	Val	Glu	Pro	Glu	
			165						170					175		
Asp	Ile	Asp	Cys	Trp	Cys	Asn	Leu	Thr	Ser	Thr	Trp	Val	Thr	Tyr	Gly	
		180						185					190			
Thr	Cys	Asn	Gln	Ala	Gly	Glu	His	Arg	Arg	Asp	Lys	Arg	Ser	Val	Ala	
		195					200					205				
Leu	Ala	Pro	His	Val	Gly	Met	Gly	Leu	Asp	Thr	Arg	Thr	Gln	Thr	Trp	
	210				215						220					
Met	Ser	Ala	Glu	Gly	Ala	Trp	Arg	Gln	Val	Glu	Lys	Val	Glu	Thr	Trp	
			225		230					235					240	
Ala	Leu	Arg	His	Pro	Gly	Phe	Thr	Ile	Leu	Ala	Leu	Phe	Leu	Ala	His	
			245						250					255		
Tyr	Ile	Gly	Thr	Ser	Leu	Thr	Gln	Lys	Val	Val	Ile	Phe	Ile	Leu	Leu	
		260						265					270			
Met	Leu	Val	Thr	Pro	Ser	Met	Thr	Met	Arg	Cys	Val	Gly	Val	Gly	Asn	
	275						280					285				
Arg	Asp	Phe	Val	Glu	Gly	Leu	Ser	Gly	Ala	Thr	Trp	Val	Asp	Val	Val	
	290					295					300					
Leu	Glu	His	Gly	Gly	Cys	Val	Thr	Thr	Met	Ala	Lys	Asn	Lys	Pro	Thr	
	305				310					315					320	
Leu	Asp	Ile	Glu	Leu	Gln	Lys	Thr	Glu	Ala	Thr	Gln	Leu	Ala	Thr	Leu	
			325						330					335		
Arg	Lys	Leu	Cys	Ile	Glu	Gly	Lys	Ile	Thr	Asn	Ile	Thr	Thr	Asp	Ser	
		340						345					350			
Arg	Cys	Pro	Thr	Gln	Gly	Glu	Ala	Ile	Leu	Pro	Glu	Glu	Gln	Asp	Gln	
		355				360						365				
Asn	Tyr	Val	Cys	Lys	His	Thr	Tyr	Val	Asp	Arg	Gly	Trp	Gly	Asn	Gly	
	370					375					380					
Cys	Gly	Leu	Phe	Gly	Lys	Gly	Ser	Leu	Val	Thr	Cys	Ala	Lys	Phe	Gln	
			385		390					395					400	
Cys	Leu	Glu	Ser	Ile	Glu	Gly	Lys	Val	Val	Gln	His	Glu	Asn	Leu	Lys	
			405						410					415		
Tyr	Thr	Val	Ile	Ile	Thr	Val	His	Thr	Gly	Asp	Gln	His	Gln	Val	Gly	
		420						425					430			
Asn	Glu	Thr	Gln	Gly	Val	Thr	Ala	Glu	Ile	Thr	Pro	Gln	Ala	Ser	Thr	
		435					440					445				
Ala	Glu	Ala	Ile	Leu	Pro	Glu	Tyr	Gly	Thr	Leu	Gly	Leu	Glu	Cys	Ser	
	450					455				460						
Pro	Arg	Thr	Gly	Leu	Asp	Phe	Asn	Glu	Met	Ile	Ser	Leu	Thr	Met	Lys	
			465		470					475					480	
Asn	Lys	Ala	Trp	Met	Val	His	Arg	Gln	Trp	Phe	Phe	Asp	Leu	Pro	Leu	
			485						490					495		
Pro	Trp	Thr	Ser	Gly	Ala	Thr	Ala	Glu	Thr	Pro	Thr	Trp	Asn	Arg	Lys	
			500					505					510			

Glu Leu Leu Val Thr Phe Lys Asn Ala His Ala Lys Lys Gln Glu Val
 515 520 525
 Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu Thr Gly
 530 535 540
 Ala Thr Glu Ile Gln Thr Ser Gly Gly Thr Ser Ile Phe Ala Gly His
 545 550 555 560
 Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Glu Leu Lys Gly Met Ser
 565 570 575
 Tyr Ala Met Cys Leu Ser Ser Phe Val Leu Lys Lys Glu Val Ser Glu
 580 585 590
 Thr Gln His Gly Thr Ile Leu Ile Lys Val Glu Tyr Lys Gly Glu Asp
 595 600 605
 Ala Pro Cys Lys Ile Pro Phe Ser Thr Glu Asp Gly Gln Gly Lys Ala
 610 615 620
 Leu Asn Gly Arg Leu Ile Thr Ala Asn Pro Val Val Thr Lys Lys Glu
 625 630 635 640
 Glu Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Glu Ser Asn Ile
 645 650 655
 Val Ile Gly Ile Gly Asp Lys Ala Leu Lys Ile Asn Trp Tyr Lys Lys
 660 665 670
 Gly Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly Ala Arg
 675 680 685
 Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser Val Gly
 690 695 700
 Gly Val Leu Asn Ser Leu Gly Lys Met Val His Gln Ile Phe Gly Ser
 705 710 715 720
 Ala Tyr Thr Ala Leu Phe Gly Gly Val Ser Trp Met Met Lys Ile Gly
 725 730 735
 Ile Gly Val Leu Leu Thr Trp Ile Gly Leu Asn Ser Lys Asn Thr Ser
 740 745 750
 Met Ser Phe Ser Cys Ile Ala Ala Gly Ile Val Thr Leu Tyr Leu Gly
 755 760 765
 Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys Asn Lys
 770 775 780
 Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val His Thr
 785 790 795 800
 Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys Leu Ala
 805 810 815
 Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile Arg Ser
 820 825 830
 Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro Glu Leu
 835 840 845
 Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met Thr Gly
 850 855 860
 Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg Pro Gln
 865 870 875 880
 Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala Lys Met
 885 890 895
 Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly Pro Glu
 900 905 910
 Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu Glu Val
 915 920 925
 Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu Lys Leu
 930 935 940

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Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser Ala Ala
 945 950 955 960
 Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp Ile Glu
 965 970 975
 Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe Ile Glu
 980 985 990
 Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser Asn Gly
 995 1000 1005
 Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala Gly Pro Val
 1010 1015 1020
 Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr Gly Pro
 1025 1030 1035 1040
 Trp His Leu Gly Lys Leu Glu Met Asp Phe Asp Phe Cys Asp Gly Thr
 1045 1050 1055
 Thr Val Val Val Thr Glu Asp Cys Gly Asn Arg Gly Pro Ser Leu Arg
 1060 1065 1070
 Thr Thr Thr Ala Ser Gly Lys Leu Ile Thr Glu Trp Cys Cys Arg Ser
 1075 1080 1085
 Cys Thr Leu Pro Pro Leu Arg Tyr Arg Gly Glu Asp Gly Cys Trp Tyr
 1090 1095 1100
 Gly Met Glu Ile Arg Pro Leu Lys Glu Lys Glu Asn Leu Val Asn
 1105 1110 1115 1120
 Ser Leu Val Thr Ala Gly His Gly Gln Val Asp Asn Phe Ser Leu Gly
 1125 1130 1135
 Val Leu Gly Met Ala Leu Phe Leu Glu Glu Met Leu Arg Thr Arg Val
 1140 1145 1150
 Gly Thr Lys His Ala Ile Leu Leu Val Ala Val Ser Phe Val Thr Leu
 1155 1160 1165
 Ile Thr Gly Asn Met Ser Phe Arg Asp Leu Gly Arg Val Met Val Met
 1170 1175 1180
 Val Gly Ala Thr Met Thr Asp Asp Ile Gly Met Gly Val Thr Tyr Leu
 1185 1190 1195 1200
 Ala Leu Leu Ala Ala Phe Lys Val Arg Pro Thr Phe Ala Ala Gly Leu
 1205 1210 1215
 Leu Leu Arg Lys Leu Thr Ser Lys Glu Leu Met Met Thr Thr Ile Gly
 1220 1225 1230
 Ile Val Leu Leu Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu Glu Leu
 1235 1240 1245
 Thr Asp Ala Leu Ala Leu Gly Met Met Val Leu Lys Met Val Arg Asn
 1250 1255 1260
 Met Glu Lys Tyr Gln Leu Ala Val Thr Ile Met Ala Ile Leu Cys Val
 1265 1270 1275 1280
 Pro Asn Ala Val Ile Leu Gln Asn Ala Trp Lys Val Ser Cys Thr Ile
 1285 1290 1295
 Leu Ala Val Val Ser Val Ser Pro Leu Phe Leu Thr Ser Ser Gln Gln
 1300 1305 1310
 Lys Thr Asp Trp Ile Pro Leu Ala Leu Thr Ile Lys Gly Leu Asn Pro
 1315 1320 1325
 Thr Ala Ile Phe Leu Thr Thr Leu Ser Arg Thr Ser Lys Lys Arg Ser
 1330 1335 1340
 Trp Pro Leu Asn Glu Ala Ile Met Ala Val Gly Met Val Ser Ile Leu
 1345 1350 1355 1360
 Ala Ser Ser Leu Leu Lys Asn Asp Ile Pro Met Thr Gly Pro Leu Val
 1365 1370 1375

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Ala Gly Gly Leu Leu Thr Val Cys Tyr Val Leu Thr Gly Arg Ser Ala
 1380 1385 1390
 Asp Leu Glu Leu Glu Arg Ala Ala Asp Val Lys Trp Glu Asp Gln Ala
 1395 1400 1405
 Glu Ile Ser Gly Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser Glu Asp
 1410 1415 1420
 Gly Ser Met Ser Ile Lys Asn Glu Glu Glu Glu Gln Thr Leu Thr Ile
 1425 1430 1435 1440
 Leu Ile Arg Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro Val Ser
 1445 1450 1455
 Ile Pro Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys Lys Gln
 1460 1465 1470
 Arg Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Met Gly Lys
 1475 1480 1485
 Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys Gly Ile Leu
 1490 1495 1500
 Gly Tyr Ser Gln Ile Gly Ala Gly Val Tyr Lys Glu Gly Thr Phe His
 1505 1510 1515 1520
 Thr Met Trp His Val Thr Arg Gly Ala Val Leu Met His Lys Gly Lys
 1525 1530 1535
 Arg Ile Glu Pro Ser Trp Ala Asp Val Lys Lys Asp Leu Ile Ser Tyr
 1540 1545 1550
 Gly Gly Gly Trp Lys Leu Glu Gly Glu Trp Lys Glu Gly Glu Glu Val
 1555 1560 1565
 Gln Val Leu Ala Leu Glu Pro Gly Lys Asn Pro Arg Ala Val Gln Thr
 1570 1575 1580
 Lys Pro Gly Leu Phe Lys Thr Asn Ala Gly Thr Ile Gly Ala Val Ser
 1585 1590 1595 1600
 Leu Asp Phe Ser Pro Gly Thr Ser Gly Ser Pro Ile Ile Asp Lys Lys
 1605 1610 1615
 Gly Lys Val Val Gly Leu Tyr Gly Asn Gly Val Val Thr Arg Ser Gly
 1620 1625 1630
 Ala Tyr Val Ser Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn
 1635 1640 1645
 Pro Glu Ile Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met
 1650 1655 1660
 Asp Leu His Pro Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro Ala Ile
 1665 1670 1675 1680
 Val Arg Glu Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro
 1685 1690 1695
 Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu Pro
 1700 1705 1710
 Ile Arg Tyr Gln Thr Pro Ala Ile Arg Ala Val His Thr Gly Arg Glu
 1715 1720 1725
 Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg Leu Leu Ser
 1730 1735 1740
 Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu Ala His
 1745 1750 1755 1760
 Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg
 1765 1770 1775
 Val Glu Met Gly Glu Ala Ala Gly Ile Phe Met Thr Ala Thr Pro Pro
 1780 1785 1790
 Gly Ser Arg Asp Pro Phe Pro Gln Ser Asn Ala Pro Ile Ile Asp Glu
 1795 1800 1805

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Glu Arg Glu Ile Pro Glu Arg Ser Trp Asn Ser Gly His Glu Trp Val
 1810 1815 1820
 Thr Asp Phe Lys Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys Ala
 1825 1830 1835 1840
 Gly Asn Asp Ile Ala Ala Cys Leu Arg Lys Asn Gly Lys Lys Val Ile
 1845 1850 1855
 Gln Leu Ser Arg Lys Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr
 1860 1865 1870
 Asn Asp Trp Asp Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala
 1875 1880 1885
 Asn Phe Lys Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro
 1890 1895 1900
 Val Ile Leu Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met
 1905 1910 1915 1920
 Pro Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg
 1925 1930 1935
 Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro Leu
 1940 1945 1950
 Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met Leu Leu
 1955 1960 1965
 Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met Phe Glu Pro
 1970 1975 1980
 Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu Arg Gly
 1985 1990 1995 2000
 Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg Arg Gly Asp Leu Pro
 2005 2010 2015
 Val Trp Leu Ala Tyr Arg Val Ala Ala Glu Gly Ile Asn Tyr Ala Asp
 2020 2025 2030
 Arg Arg Trp Cys Phe Asp Gly Val Lys Asn Asn Gln Ile Leu Glu Glu
 2035 2040 2045
 Asn Val Glu Val Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys Lys Leu
 2050 2055 2060
 Lys Pro Arg Trp Leu Asp Ala Arg Ile Tyr Ser Asp Pro Leu Ala Leu
 2065 2070 2075 2080
 Lys Glu Phe Lys Glu Phe Ala Ala Gly Arg Lys Ser Leu Thr Leu Asn
 2085 2090 2095
 Leu Ile Thr Glu Met Gly Arg Leu Pro Thr Phe Met Thr Gln Lys Ala
 2100 2105 2110
 Arg Asp Ala Leu Asp Asn Leu Ala Val Leu His Thr Ala Glu Ala Gly
 2115 2120 2125
 Gly Arg Ala Tyr Asn His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu
 2130 2135 2140
 Thr Leu Leu Leu Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe
 2145 2150 2155 2160
 Leu Phe Leu Met Ser Ala Arg Gly Ile Gly Lys Met Thr Leu Gly Met
 2165 2170 2175
 Cys Cys Ile Ile Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln Ile Gln
 2180 2185 2190
 Pro His Trp Ile Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Ile Val
 2195 2200 2205
 Leu Leu Ile Pro Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn Gln
 2210 2215 2220
 Leu Thr Tyr Val Val Ile Ala Ile Leu Thr Val Val Ala Ala Thr Met
 2225 2230 2235 2240

Ala	Asn	Glu	Met	Gly	Phe	Leu	Glu	Lys	Thr	Lys	Lys	Asp	Leu	Gly	Leu	
				2245					2250						2255	
Gly	Ser	Ile	Ala	Thr	Gln	Gln	Pro	Glu	Ser	Asn	Ile	Leu	Asp	Ile	Asp	
			2260					2265					2270			
Leu	Arg	Pro	Ala	Ser	Ala	Trp	Thr	Leu	Tyr	Ala	Val	Ala	Thr	Thr	Phe	
			2275				2280					2285				
Val	Thr	Pro	Met	Leu	Arg	His	Ser	Ile	Glu	Asn	Ser	Ser	Val	Asn	Val	
			2290			2295					2300					
Ser	Leu	Thr	Ala	Ile	Ala	Asn	Gln	Ala	Thr	Val	Leu	Met	Gly	Leu	Gly	
2305				2310				2315						2320		
Lys	Gly	Trp	Pro	Leu	Ser	Lys	Met	Asp	Ile	Gly	Val	Pro	Leu	Leu	Ala	
			2325					2330						2335		
Ile	Gly	Cys	Tyr	Ser	Gln	Val	Asn	Pro	Ile	Thr	Leu	Thr	Ala	Ala	Leu	
			2340				2345						2350			
Phe	Leu	Leu	Val	Ala	His	Tyr	Ala	Ile	Ile	Gly	Pro	Gly	Leu	Gln	Ala	
			2355			2360						2365				
Lys	Ala	Thr	Arg	Glu	Ala	Gln	Lys	Arg	Ala	Ala	Ala	Gly	Ile	Met	Lys	
			2370			2375				2380						
Asn	Pro	Thr	Val	Asp	Gly	Ile	Thr	Val	Ile	Asp	Leu	Asp	Pro	Ile	Pro	
2385				2390				2395						2400		
Tyr	Asp	Pro	Lys	Phe	Glu	Lys	Gln	Leu	Gly	Gln	Val	Met	Leu	Leu	Val	
			2405					2410						2415		
Leu	Cys	Val	Thr	Gln	Val	Leu	Met	Met	Arg	Thr	Thr	Trp	Ala	Leu	Cys	
			2420					2425					2430			
Glu	Ala	Leu	Thr	Leu	Ala	Thr	Gly	Pro	Ile	Ser	Thr	Leu	Trp	Glu	Gly	
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Asn	Pro	Gly	Arg	Phe	Trp	Asn	Thr	Thr	Ile	Ala	Val	Ser	Met	Ala	Asn	
			2450			2455					2460					
Ile	Phe	Arg	Gly	Ser	Tyr	Leu	Ala	Gly	Ala	Gly	Leu	Leu	Phe	Ser	Ile	
2465				2470				2475						2480		
Met	Lys	Asn	Thr	Thr	Asn	Thr	Arg	Arg	Gly	Thr	Gly	Asn	Ile	Gly	Glu	
			2485					2490					2495			
Thr	Leu	Gly	Glu	Lys	Trp	Lys	Ser	Arg	Leu	Asn	Ala	Leu	Gly	Lys	Ser	
			2500					2505					2510			
Glu	Phe	Gln	Ile	Tyr	Lys	Lys	Ser	Gly	Ile	Gln	Glu	Val	Asp	Arg	Thr	
			2515				2520					2525				
Leu	Ala	Lys	Glu	Gly	Ile	Lys	Arg	Gly	Glu	Thr	Asp	His	His	Ala	Val	
			2530			2535				2540						
Ser	Arg	Gly	Ser	Ala	Lys	Leu	Arg	Trp	Phe	Val	Glu	Arg	Asn	Met	Val	
2545				2550					2555					2560		
Thr	Pro	Glu	Gly	Lys	Val	Val	Asp	Leu	Gly	Cys						

121

Asn Pro Tyr Met Pro Ser Val Ile Glu Lys Met Glu Ala Leu Gln Arg
 2675 2680 2685
 Lys Tyr Gly Gly Ala Leu Val Arg Asn Pro Leu Ser Arg Asn Ser Thr
 2690 2695 2700
 His Glu Met Tyr Trp Val Ser Asn Ala Ser Gly Asn Ile Val Ser Ser
 2705 2710 2715 2720
 Val Asn Met Ile Ser Arg Met Leu Ile Asn Arg Phe Thr Met Arg Tyr
 2725 2730 2735
 Lys Lys Ala Thr Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly Thr Arg
 2740 2745 2750
 Asn Ile Gly Ile Glu Ser Glu Ile Pro Asn Leu Asp Ile Ile Gly Lys
 2755 2760 2765
 Arg Ile Glu Lys Ile Lys Gln Glu His Glu Thr Ser Trp His Tyr Asp
 2770 2775 2780
 Gln Asp His Pro Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Thr
 2785 2790 2795 2800
 Lys Gln Thr Gly Ser Ala Ser Ser Met Val Asn Gly Val Val Arg Leu
 2805 2810 2815
 Leu Thr Lys Pro Trp Asp Val Val Pro Met Val Thr Gln Met Ala Met
 2820 2825 2830
 Thr Asp Thr Thr Pro Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val
 2835 2840 2845
 Asp Thr Arg Thr Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu Met Lys
 2850 2855 2860
 Ile Thr Ala Glu Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys Thr Pro
 2865 2870 2875 2880
 Arg Met Cys Thr Arg Glu Glu Phe Thr Arg Lys Val Arg Ser Asn Ala
 2885 2890 2895
 Ala Leu Gly Ala Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser Ala Arg
 2900 2905 2910
 Glu Ala Val Glu Asp Ser Arg Phe Trp Glu Leu Val Asp Lys Glu Arg
 2915 2920 2925
 Asn Leu His Leu Glu Gly Lys Cys Glu Thr Cys Val Tyr Asn Met Met
 2930 2935 2940
 Gly Lys Arg Glu Lys Lys Leu Gly Glu Phe Gly Lys Ala Lys Gly Ser
 2945 2950 2955 2960
 Arg Ala Ile Trp Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu Phe Glu
 2965 2970 2975
 Ala Leu Gly Phe Leu Asn Glu Asp His Trp Phe Ser Arg Glu Asn Ser
 2980 2985 2990
 Leu Ser Gly Val Glu Gly Glu Gly Leu His Lys Leu Gly Tyr Ile Leu
 2995 3000 3005
 Arg Asp Val Ser Lys Lys Glu Gly Gly Ala Met Tyr Ala Asp Asp Thr
 3010 3015 3020
 Ala Gly Trp Asp Thr Arg Ile Thr Leu Glu Asp Leu Lys Asn Glu Glu
 3025 3030 3035 3040
 Met Val Thr Asn His Met Glu Gly Glu His Lys Lys Leu Ala Glu Ala
 3045 3050 3055
 Ile Phe Lys Leu Thr Tyr Gln Asn Lys Val Val Arg Val Gln Arg Pro
 3060 3065 3070
 Thr Pro Arg Gly Thr Val Met Asp Ile Ile Ser Arg Arg Asp Gln Arg
 3075 3080 3085
 Gly Ser Gly Gln Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met
 3090 3095 3100

122

Glu Ala Gln Leu Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser
 3105 3110 3115 3120
 Ile Gln His Leu Thr Ile Thr Glu Glu Ile Ala Val Gln Asn Trp Leu
 3125 3130 3135
 Ala Arg Val Gly Arg Glu Arg Leu Ser Arg Met Ala Ile Ser Gly Asp
 3140 3145 3150
 Asp Cys Val Val Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala Leu Thr
 3155 3160 3165
 Ala Leu Asn Asp Met Gly Lys Ile Arg Lys Asp Ile Gln Gln Trp Glu
 3170 3175 3180
 Pro Ser Arg Gly Trp Asn Asp Trp Thr Gln Val Pro Phe Cys Ser His
 3185 3190 3195 3200
 His Phe His Glu Leu Ile Met Lys Asp Gly Arg Val Leu Val Val Pro
 3205 3210 3215
 Cys Arg Asn Gln Asp Glu Leu Ile Gly Arg Ala Arg Ile Ser Gln Gly
 3220 3225 3230
 Ala Gly Trp Ser Leu Arg Glu Thr Ala Cys Leu Gly Lys Ser Tyr Ala
 3235 3240 3245
 Gln Met Trp Ser Leu Met Tyr Phe His Arg Arg Asp Leu Arg Leu Ala
 3250 3255 3260
 Ala Asn Ala Ile Cys Ser Ala Val Pro Ser His Trp Val Pro Thr Ser
 3265 3270 3275 3280
 Arg Thr Thr Trp Ser Ile His Ala Lys His Glu Trp Met Thr Thr Glu
 3285 3290 3295
 Asp Met Leu Thr Val Trp Asn Arg Val Trp Ile Gln Glu Asn Pro Trp
 3300 3305 3310
 Met Glu Asp Lys Thr Pro Val Glu Ser Trp Glu Glu Ile Pro Tyr Leu
 3315 3320 3325
 Gly Lys Arg Glu Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser
 3330 3335 3340
 Arg Ala Thr Trp Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln Val Arg
 3345 3350 3355 3360
 Ser Leu Ile Gly Asn Glu Glu Tyr Thr Asp Tyr Met Pro Ser Met Lys
 3365 3370 3375
 Arg Phe Arg Arg Glu Glu Glu Ala Gly Val Leu Trp
 3380 3385

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<211> 10723

<212> DNA

<213> Artificial Sequence

<220>

 <223> Description of Artificial Sequence:/Note =
 synthetic construct

<221> CDS

<222> (97)...(1072)

<400> 11

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60.

123

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				Met	Asn	Asn	Gln	Arg	Lys		
				1				5			
aag	gcg	aaa	aac	acg	cct	ttc	aat	atg	ctg	aaa	162
Lys	Ala	Lys	Asn	Thr	Pro	Phe	Asn	Met	Leu	Lys	
			10					15		20	
gtg	tcg	act	gtg	caa	cag	ctg	aca	aag	aga	ttc	210
Val	Ser	Thr	Val	Gln	Gln	Leu	Thr	Lys	Arg	Phe	
			25				30			35	
cag	gga	cga	gga	cca	tta	aaa	ctg	ttc	atg	gcc	258
Gln	Gly	Arg	Gly	Pro	Leu	Lys	Leu	Phe	Met	Ala	
			40			45				50	
cgt	ttc	cta	aca	atc	cca	cca	aca	gca	ggg	ata	306
Arg	Phe	Leu	Thr	Ile	Pro	Pro	Thr	Ala	Gly	Ile	
			55			60			65	70	
aca	att	aaa	aaa	tca	aaa	gct	att	aat	gtt	ttg	354
Thr	Ile	Lys	Lys	Ser	Lys	Ala	Ile	Asn	Val	Leu	
				75				80			
gag	att	gga	agg	atg	ctg	aac	atc	ttg	aat	agg	402
Glu	Ile	Gly	Arg	Met	Leu	Asn	Ile	Leu	Asn	Arg	
				90				95			
ggc	atg	atc	att	atg	ctg	att	cca	aca	gtg	atg	450
Gly	Met	Ile	Ile	Met	Leu	Ile	Pro	Thr	Val	Met	
			105				110				
acg	cgt	gat	ggc	gaa	ccc	ctc	atg	ata	gtg	gca	498
Thr	Arg	Asp	Gly	Glu	Pro	Leu	Met	Ile	Val	Ala	
			120			125				130	
aga	cct	ctc	ttg	ttt	aag	aca	aca	gag	ggg	atc	546
Arg	Pro	Leu	Leu	Phe	Lys	Thr	Thr	Glu	Gly	Ile	
			135			140			145		
att	gcc	atg	gac	ttg	ggt	gaa	atg	tgt	gag	gac	594
Ile	Ala	Met	Asp	Leu	Gly	Glu	Met	Cys	Glu	Asp	
			155					160			
tgc	ccc	tta	ctg	gtc	aat	acc	gaa	cct	gaa	gac	642
Cys	Pro	Leu	Leu	Val	Asn	Thr	Glu	Pro	Glu	Asp	
			170				175				
aat	ctc	acg	tct	acc	tgg	gtc	atg	tat	ggg	aca	690
Asn	Leu	Thr	Ser	Thr	Trp	Val	Met	Tyr	Gly	Thr	
			185				190				
gaa	cgg	aga	cga	gag	aag	cgc	tca	gta	gct	tta	738
Glu	Arg	Arg	Arg	Glu	Lys	Arg	Ser	Val	Ala	Leu	
			200			205				210	

124

atg gga ttg gaa aca aga gct gag aca tgg atg tca tcg gaa ggg gct Met Gly Leu Glu Thr Arg Ala Glu Thr Trp Met Ser Ser Glu Gly Ala 215 220 225 230	786
tgg aag cat gct cag aga gta gag agc tgg ata ctc aga aac cca gga Trp Lys His Ala Gln Arg Val Glu Ser Trp Ile Leu Arg Asn Pro Gly 235 240 245	834
ttc gcg ctc ttg gca gga ttt atg gct tat atg att ggg caa aca gga Phe Ala Leu Leu Ala Gly Phe Met Ala Tyr Met Ile Gly Gln Thr Gly 250 255 260	882
atc cag cga act gtc ttc ttt gtc cta atg atg ctg gtc gcc cca tcc Ile Gln Arg Thr Val Phe Phe Val Leu Met Met Leu Val Ala Pro Ser 265 270 275	930
tac gga atg cga tgc gta gga gta gga aac aga gac ttt gtg gaa gga Tyr Gly Met Arg Cys Val Gly Val Gly Asn Arg Asp Phe Val Glu Gly 280 285 290	978
gtc tca ggt gga gca tgg gtc gat ctg gtg cta gaa cat gga gga tgc Val Ser Gly Gly Ala Trp Val Asp Leu Val Leu Glu His Gly Gly Cys 295 300 305 310	1026
gtc aca acc atg gcc cag gga aaa cca acc ttg gat ttt gaa ctg act Val Thr Thr Met Ala Gln Gly Lys Pro Thr Leu Asp Phe Glu Leu Thr 315 320 325	1074
aag aca aca gcc aag gaa gtg gct ctg tta aga acc tat tgc att gaa Lys Thr Thr Ala Lys Glu Val Ala Leu Leu Arg Thr Tyr Cys Ile Glu 330 335 340	1122
gcc tca ata tca aac ata acc acg gca aca aga tgt cca acg caa gga Ala Ser Ile Ser Asn Ile Thr Thr Ala Thr Arg Cys Pro Thr Gln Gly 345 350 355	1170
gag cct tat cta aaa gag gaa caa gac caa cag tac att tgc cgg aga Glu Pro Tyr Leu Lys Glu Glu Gln Asp Gln Gln Tyr Ile Cys Arg Arg 360 365 370	1218
gat gtg gta gac aga ggg tgg ggc aat ggc tgt ggc ttg ttt gga aaa Asp Val Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly Lys 375 380 385 390	1266
gga gga gtt gtg aca tgt gcg aag ttt tca tgt tcg ggg aag ata aca Gly Gly Val Val Thr Cys Ala Lys Phe Ser Cys Ser Gly Lys Ile Thr 395 400 405	1314
ggc aat ttg gtc caa att gag aac ctt gaa tac aca gtg gtt gta aca Gly Asn Leu Val Gln Ile Glu Asn Leu Glu Tyr Thr Val Val Val Thr 410 415 420	1362

125

gtc cac aat gga gac acc cat gca gta gga aat gac acg tcc aat cat	1410
Val His Asn Gly Asp Thr His Ala Val Gly Asn Asp Thr Ser Asn His	
425 430 435	
gga gtt aca gcc acg ata act ccc agg tca cca tgc gtg gaa gtc aaa	1458
Gly Val Thr Ala Thr Ile Thr Pro Arg Ser Pro Ser Val Glu Val Lys	
440 445 450	
ttg cgg gac tat gga gaa cta aca ctc gat tgt gaa ccc agg tct gga	1506
Leu Pro Asp Tyr Gly Glu Leu Thr Leu Asp Cys Glu Pro Arg Ser Gly	
455 460 465 470	
att gac ttt aat gag atg att ctg atg aaa atg aaa aag aaa aca tgg	1554
Ile Asp Phe Asn Glu Met Ile Leu Met Lys Met Lys Lys Lys Thr Trp	
475 480 485	
ctt gtg cat aag caa tgg ttt ttg gat cta cct cta cca tgg aca gca	1602
Leu Val His Lys Gln Trp Phe Leu Asp Leu Pro Leu Pro Trp Thr Ala	
490 495 500	
gga gca gac aca tca gag gtt cac tgg aat tac aaa gag aga atg gtg	1650
Gly Ala Asp Thr Ser Glu Val His Trp Asn Tyr Lys Glu Arg Met Val	
505 510 515	
aca ttt aag gtt cct cat gcc aag aga cag gat gtg aca gtg ctg gga	1698
Thr Phe Lys Val Pro His Ala Lys Arg Gln Asp Val Thr Val Leu Gly	
520 525 530	
tct cag gaa gga gcc atg cat tct gcc ctc gct gga gcc aca gaa gtg	1746
Ser Gln Glu Gly Ala Met His Ser Ala Leu Ala Gly Ala Thr Glu Val	
535 540 545 550	
gac tcc ggt gat gga aat cac atg ttt gca gga cat ctc aag tgc aaa	1794
Asp Ser Gly Asp Gly Asn His Met Phe Ala Gly His Leu Lys Cys Lys	
555 560 565	
gtc cgt atg gag aaa ttg aga atc aag gga atg tca tac acg atg tgt	1842
Val Arg Met Glu Lys Leu Arg Ile Lys Gly Met Ser Tyr Thr Met Cys	
570 575 580	
tca gga aag ttc tca att gac aaa gag atg gca gaa aca cag cat ggg	1890
Ser Gly Lys Phe Ser Ile Asp Lys Glu Met Ala Glu Thr Gln His Gly	
585 590 595	
aca aca gtg gtg aaa gtc aag tat gaa ggt gct gga gct cgg tgt aaa	1938
Thr Thr Val Val Lys Val Lys Tyr Glu Gly Ala Gly Ala Pro Cys Lys	
600 605 610	
gtc ccc ata gag ata aga gat gtg aac aag gaa aaa gtg gtt ggg cgt	1986
Val Pro Ile Glu Ile Arg Asp Val Asn Lys Glu Lys Val Val Gly Arg	
615 620 625 630	
atc atc tca tcc acc cct ttg gct gag aat acc aac agt gta acc aac	2034
Ile Ile Ser Ser Thr Pro Leu Ala Glu Asn Thr Asn Ser Val Thr Asn	
635 640 645	

ata gag tta gaa ccc ccc ttt ggg gac agc tac ata gtg ata ggt gtt Ile Glu Leu Glu Pro Pro Phe Gly Asp Ser Tyr Ile Val Ile Gly Val 650 655 660	2082
gga aac agt gca tta aca ctc cat tgg ttc agg aaa ggg agt tcc att Gly Asn Ser Ala Leu Thr Leu His Trp Phe Arg Lys Gly Ser Ser Ile 665 670 675	2130
ggc aag atg ttt gag tcc aca tac aga ggt gca aaa cga atg gcc att Gly Lys Met Phe Glu Ser Thr Tyr Arg Gly Ala Lys Arg Met Ala Ile 680 685 690	2178
cta ggt gaa aca gct tgg gat ttt ggt tcc gtt ggt gga ctg ttc aca Leu Gly Glu Thr Ala Trp Asp Phe Gly Ser Val Gly Gly Leu Phe Thr 695 700 705 710	2226
tca ttg gga aag gct gtg cac cag gtt ttt gga agt gtg tat aca acc Ser Leu Gly Lys Ala Val His Gln Val Phe Gly Ser Val Tyr Thr Thr 715 720 725	2274
ctg ttt gga gga gtc tca tgg atg att aga atc cta att ggg ttc cta Leu Phe Gly Gly Val Ser Trp Met Ile Arg Ile Leu Ile Gly Phe Leu 730 735 740	2322
gtg ttg tgg att ggc acg aac tca agg aac act tca atg gct atg acg Val Leu Trp Ile Gly Thr Asn Ser Arg Asn Thr Ser Met Ala Met Thr 745 750 755	2370
tgc ata gct gcc ggc att gtg aca ctg tat ttg gga gtc atg gtg cag Cys Ile Ala Ala Gly Ile Val Thr Leu Tyr Leu Gly Val Met Val Gln 760 765 770	2418
gcc gat agt ggt tgc gtt gtg agc tgg aaa aac aaa gaa ctg aaa tgt Ala Asp Ser Gly Cys Val Val Ser Trp Lys Asn Lys Glu Leu Lys Cys 775 780 785 790	2466
ggc agt ggg att ttc atc aca gac aac gtg cac aca tgg aca gaa .caa Gly Ser Gly Ile Phe Ile Thr Asp Asn Val His Thr Trp Thr Glu Gln 795 800 805	2514
tac aag ttc caa cca gaa tcc cct tca aaa cta gct tca gct atc cag Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys Leu Ala Ser Ala Ile Gln 810 815 820	2562
aaa gcc cat gaa gag gac att tgt gga atc cgc tca gta aca aga ctg Lys Ala His Glu Glu Asp Ile Cys Gly Ile Arg Ser Val Thr Arg Leu 825 830 835	2610
gag aat ctg atg tgg aaa caa ata aca cca gaa ttg aat cac att cta Glu Asn Leu Met Trp Lys Gln Ile Thr Pro Glu Leu Asn His Ile Leu 840 845 850	2658

127

tca gaa aat gag gtg aag tta act att atg aca gga gac atc aaa gga Ser Glu Asn Glu Val Lys Leu Thr Ile Met Thr Gly Asp Ile Lys Gly 855 860 865 870	2706
atc atg cag gca gga aaa cga tct ctg cgg cct cag ccc act gag ctg Ile Met Gln Ala Gly Lys Arg Ser Leu Arg Pro Gln Pro Thr Glu Leu 875 880 885	2754
aag tat tca tgg aaa aca tgg ggc aaa gca aaa atg ctc tct aca gag Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala Lys Met Leu Ser Thr Glu 890 895 900	2802
tct cat aac cag acc ttt ctc att gat ggc ccc gaa aca gca gaa tgc Ser His Asn Gln Thr Phe Leu Ile Asp Gly Pro Glu Thr Ala Glu Cys 905 910 915	2850
ccc aac aca aat aga gct tgg aat tgg ttg gaa gtt gaa gac tat ggc Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu Glu Val Glu Asp Tyr Gly 920 925 930	2898
ttt gga gta ttc acc acc aat ata tgg cta aaa ttg aaa gaa aaa cag Phe Gly Val Phe Thr Thr Asn Ile Trp Leu Lys Leu Lys Glu Lys Gln 935 940 945 950	2946
gat gta ttc tgc gac tca aaa ctc atg tca gcg gcc ata aaa gac aac Asp Val Phe Cys Asp Ser Lys Leu Met Ser Ala Ala Ile Lys Asp Asn 955 960 965	2994
aga gcc gtc cat gcc gat atg ggt tat tgg ata gaa agt gca ctc aat Arg Ala Val His Ala Asp Met Gly Tyr Trp Ile Glu Ser Ala Leu Asn 970 975 980	3042
gac aca tgg aag ata gag aaa gcc tct ttc att gaa gtt aaa aac tgc Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe Ile Glu Val Lys Asn Cys 985 990 995	3090
cac tgg cca aaa tca cac acc ctc tgg agc aat gga gtg cta gaa agt His Trp Pro Lys Ser His Thr Leu Trp Ser Asn Gly Val Leu Glu Ser 1000 1005 1010	3138
gag atg ata att cca aag aat ctc gct gga cca gtg tct caa cac aac Glu Met Ile Ile Pro Lys Asn Leu Ala Gly Pro Val Ser Gln His Asn 1015 1020 1025 1030	3186
tat aga cca ggc tac cat aca caa ata aca gga cca tgg cat cta ggt Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr Gly Pro Trp His Leu Gly 1035 1040 1045	3234
aag ctt gag atg gac ttt gat ttc tgt gat gga aca aca gtg gta gtg Lys Leu Glu Met Asp Phe Asp Phe Cys Asp Gly Thr Thr Val Val Val 1050 1055 1060	3282
act gag gac tgc gga aat aga gga ccc tct ttg aga aca acc act gcc Thr Glu Asn Cys Gly Asn Arg Gly Pro Ser Leu Arg Thr Thr Thr Ala 1065 1070 1075	3330

128

tct gga aaa ctc ata aca gaa tgg tgc tgc cga tct tgc aca tta cca Ser Gly Lys Leu Ile Thr Glu Trp Cys Cys Arg Ser Cys Thr Leu Pro 1080 1085 1090	3378
ccg cta aga tac aga ggt gag gat ggg tgc tgg tac ggg atg gaa atc Pro Leu Arg Tyr Arg Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile 1095 1100 1105 1110	3426
aga cca ttg aag gag aaa gaa gag aat ttg gtc aac tcc ttg gtc aca Arg Pro Leu Lys Glu Lys Glu Glu Asn Leu Val Asn Ser Leu Val Thr 1115 1120 1125	3474
gct gga cat ggg cag gtc gac aac ttt tca cta gga gtc ttg gga atg Ala Gly His Gly Gln Val Asp Asn Phe Ser Leu Gly Val Leu Gly Met 1130 1135 1140	3522
gca ttg ttc ctg gag gaa atg ctt agg acc cga gta gga acg aaa cat Ala Leu Phe Leu Glu Glu Met Leu Arg Thr Arg Val Gly Thr Lys His 1145 1150 1155	3570
gca ata cta cta gtt gca gtt tct ttt gtg aca ttg atc aca ggg aac Ala Ile Leu Leu Val Ala Val Ser Phe Val Thr Leu Ile Thr Gly Asn 1160 1165 1170	3618
atg tcc ttt aga gac ctg gga aga gtg atg gtt atg gta ggc gcc act Met Ser Phe Arg Asp Leu Gly Arg Val Met Val Met Val Gly Ala Thr 1175 1180 1185 1190	3666
atg acg gat gac ata ggt atg ggc gtg act tat ctt gcc cta cta gca Met Thr Asp Asp Ile Gly Met Gly Val Thr Tyr Leu Ala Leu Leu Ala 1195 1200 1205	3714
gcc ttc aaa gtc aga cca act ttt gca gct gga cta ctc ttg aga aag Ala Phe Lys Val Arg Pro Thr Phe Ala Ala Gly Leu Leu Leu Arg Lys 1210 1215 1220	3762
ctg acc tcc aag gaa ttg atg atg act act ata gga att gta ctc ctc Leu Thr Ser Lys Glu Leu Met Met Thr Thr Ile Gly Ile Val Leu Leu 1225 1230 1235	3810
tcc cag agc acc ata cca gag acc att ctt gag ttg act gat gcg tta Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu Glu Leu Thr Asp Ala Leu 1240 1245 1250	3858
gcc tta ggc atg atg gtc ctc aaa atg gtg aga aat atg gaa aag tat Ala Leu Gly Met Met Val Leu Lys Met Val Arg Asn Met Glu Lys Tyr 1255 1260 1265 1270	3906
caa ttg gca gtg act atc atg gct atc ttg tgc gtc cca aac gca gtg Gln Leu Ala Val Thr Ile Met Ala Ile Leu Cys Val Pro Asn Ala Val 1275 1280 1285	3954

129

ata tta caa aac gca tgg aaa gtg agt tgc aca ata ttg gca gtg gtg Ile Leu Gln Asn Ala Trp Lys Val Ser Cys Thr Ile Leu Ala Val Val 1290 1295 1300	4002
tcc gtt tcc cca ctg ttc tta aca tcc tca cag caa aaa aca gat tgg Ser Val Ser Pro Leu Phe Leu Thr Ser Ser Gln Gln Lys Thr Asp Trp 1305 1310 1315	4050
ata cca tta gca ttg acg atc aaa ggt ctc aat cca aca gct att ttt Ile Pro Leu Ala Leu Thr Ile Lys Gly Leu Asn Pro Thr Ala Ile Phe 1320 1325 1330	4098
cta aca acc ctc tca aga acc agc aag aaa agg agc tgg cca tta aat Leu Thr Thr Leu Ser Arg Thr Ser Lys Arg Ser Trp Pro Leu Asn 1335 1340 1345 1350	4146
gag gct atc atg gca gtc ggg atg gtg agc att tta gcc agt tct ctc Glu Ala Ile Met Ala Val Gly Met Val Ser Ile Leu Ala Ser Ser Leu 1355 1360 1365	4194
cta aaa aat gat att ccc atg aca gga cca tta gtg gct gga ggg ctc Leu Lys Asn Asp Ile Pro Met Thr Gly Pro Leu Val Ala Gly Gly Leu 1370 1375 1380	4242
ctc act gtg tgc tac gtg ctc act gga cga tgg gcc gat ttg gaa ctg Leu Thr Val Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu Leu 1385 1390 1395	4290
gag aga gca gcc gat gtc aaa tgg gaa gac cag gca gag ata tca gga Glu Arg Ala Ala Asp Val Lys Trp Glu Asp Gln Ala Glu Ile Ser Gly 1400 1405 1410	4338
agc agt cca atc ctg tca ata aca ata tca gaa gat ggt agc atg tgg Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser Glu Asp Gly Ser Met Ser 1415 1420 1425 1430	4386
ata aaa aat gaa gag gaa gaa caa aca ctg acc ata ctc att aga aca Ile Lys Asn Glu Glu Glu Gln Thr Leu Thr Ile Leu Ile Arg Thr 1435 1440 1445	4434
gga ttg ctg gtg atc tca gga ctt ttt cct gta tca ata cca atc acg Gly Leu Leu Val Ile Ser Gly Leu Phe Pro Val Ser Ile Pro Ile Thr 1450 1455 1460	4482
gca gca gca tgg tac ctg tgg gaa gtg aag aaa caa cgg gcc gga gta Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys Lys Gln Arg Ala Gly Val 1465 1470 1475	4530
ttg tgg gat gtt cct tca ccc cca ccc atg gga aag gct gaa ctg gaa Leu Trp Asp Val Pro Ser Pro Pro Pro Met Gly Lys Ala Glu Leu Glu 1480 1485 1490	4578
gat gga gcc tat aga att aag caa aaa ggg att ctt gga tat tcc cag Asp Gly Ala Tyr Arg Ile Lys Gln Lys Gly Ile Leu Gly Tyr Ser Gln 1495 1500 1505 1510	4626

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atc gga gcc gga gtt tac aaa gaa gga aca ttc cat aca atg tgg cat Ile Gly Ala Gly Val Tyr Lys Glu Gly Thr Phe His Thr Met Trp His 1515 1520 1525	4674
gtc aca cgt ggc gct gtt cta atg cat aaa gga aag agg att gaa cca Val Thr Arg Gly Ala Val Leu Met His Lys Gly Lys Arg Ile Glu Pro 1530 1535 1540	4722
tca tgg gcg gac gtc aag aaa gac cta ata tca tat gga gga ggc tgg Ser Trp Ala Asp Val Lys Lys Asp Leu Ile Ser Tyr Gly Gly Trp 1545 1550 1555	4770
aag tta gaa gga gaa tgg aag gaa gga gaa gaa gtc cag gta ttg gca Lys Leu Glu Gly Glu Trp Lys Glu Gly Glu Glu Val Gln Val Leu Ala 1560 1565 1570	4818
ctg gag cct gga aaa aat cca aga gcc gtc caa acg aaa cct ggt ctt Leu Glu Pro Gly Lys Asn Pro Arg Ala Val Gln Thr Lys Pro Gly Leu 1575 1580 1585 1590	4866
ttc aaa acc aac gcc gga aca ata ggt gct gta tct ctg gac ttt tct Phe Lys Thr Asn Ala Gly Thr Ile Gly Ala Val Ser Leu Asp Phe Ser 1595 1600 1605	4914
cct gga acg tca gga tct cca att atc gac aaa aaa gga aaa gtt gtg Pro Gly Thr Ser Gly Ser Pro Ile Ile Asp Lys Lys Gly Lys Val Val 1610 1615 1620	4962
ggt ctt tat ggt aat ggt gtt gtt aca agg agt gga gca tat gtg agt Gly Leu Tyr Gly Asn Gly Val Val Thr Arg Ser Gly Ala Tyr Val Ser 1625 1630 1635	5010
gct ata gcc cag act gaa aaa agc att gaa gac aac cca gag atc gaa Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile Glu 1640 1645 1650	5058
gat gac att ttc cga aag aga aga ctg acc atc atg gac ctc cac cca Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu His Pro 1655 1660 1665 1670	5106
gga gcg gga aag acg aag aga tac ctt ccg gcc ata gtc aga gaa gct Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro Ala Ile Val Arg Glu Ala 1675 1680 1685	5154
ata aaa cgg ggt ttg aga aca tta atc ttg gcc ccc act aga gtt gtg Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro Thr Arg Val Val 1690 1695 1700	5202
gca gct gaa atg gag gaa gcc ctt aga gga ctt cca ata aga tac cag Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu Pro Ile Arg Tyr Gln 1705 1710 1715	5250

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acc cca gcc atc aga gct gtg cac acc ggg cgg gag att gtg gac cta Thr Pro Ala Ile Arg Ala Val His Thr Gly Arg Glu Ile Val Asp Leu 1720 1725 1730	5298
atg tgt cat gcc aca ttt acc atg agg ctg cta tca cca gtt aga gtg Met Cys His Ala Thr Phe Thr Met Arg Leu Leu Ser Pro Val Arg Val 1735 1740 1745 1750	5346
cca aac tac aac ctg att atc atg gac gaa gcc cat ttc aca gac cca Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu Ala His Phe Thr Asp Pro 1755 1760 1765	5394
gca agt ata gca gct aga gga tac atc tca act cga gtg gag atg ggt Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Glu Met Gly 1770 1775 1780	5442
gag gca gct ggg att ttt atg aca gcc act ccc ccg gga agc aga gac Glu Ala Ala Gly Ile Phe Met Thr Ala Thr Pro Pro Gly Ser Arg Asp 1785 1790 1795	5490
cca ttt cct cag agc aat gca cca atc ata gat gaa gaa aga gaa atc Pro Phe Pro Gln Ser Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu Ile 1800 1805 1810	5538
cct gaa cgc tgg tgg aat tcc gga cat gaa tgg gtc acg gat ttt aaa Pro Glu Arg Ser Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe Lys 1815 1820 1825 1830	5586
ggg aag act gtt tgg ttc gtt cca agt ata aaa gca gga aat gat ata Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile 1835 1840 1845	5634
gca gct tgc ctg agg aaa aat gga aag aaa gtg ata caa ctc agt agg Ala Ala Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg 1850 1855 1860	5682
aag acc ttt gat tct gag tat gtc aag act aga acc aat gat tgg gac Lys Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp 1865 1870 1875	5730
ttc gtg gtt aca act gac att tca gaa atg ggt gcc aat ttc aag gct Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys Ala 1880 1885 1890	5778
gag agg gtt ata gac ccc aga cgc tgc atg aaa cca gtc ata cta aca Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile Leu Thr 1895 1900 1905 1910	5826
gat ggt gaa gag cgg gtg att ctg gca gga cct atg cca gtg acc cac Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr His 1915 1920 1925	5874
tct agt gca gca caa aga aga ggg aga ata gga aga aat cca aaa aat Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro Lys Asn 1930 1935 1940	5922

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gag aat gac cag tac ata tac atg ggg gaa cct ctg gaa aat gat gaa Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro Leu Glu Asn Asp Glu 1945 1950 1955	5970
gac tgt gca cac tgg aaa gaa gct aaa atg ctc cta gat aac atc aac Asp Cys Ala His Trp Lys Glu Ala Lys Met Leu Leu Asp Asn Ile Asn 1960 1965 1970	6018
acg cca gaa gga atc att cct agc atg ttc gaa cca gag cgt gaa aag Thr Pro Glu Gly Ile Ile Pro Ser Met Phe Glu Pro Glu Arg Glu Lys 1975 1980 1985 1990	6066
gtg gat gcc att gat ggc gaa tac cgc ttg aga gga gaa gca agg aaa Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu Arg Gly Glu Ala Arg Lys 1995 2000 2005	6114
acc ttt gta gac tta atg aga aga gga gac cta cca gtc tgg ttg gcc Thr Phe Val Asp Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ala 2010 2015 2020	6162
tac aga gtg gca gct gaa ggc atc aac tac gca gac aga agg tgg tgt Tyr Arg Val Ala Ala Glu Gly Ile Asn Tyr Ala Asp Arg Arg Trp Cys 2025 2030 2035	6210
ttt gat gga gtc aag aac aac caa atc cta gaa gaa aac gtg gaa gtt Phe Asp Gly Val Lys Asn Asn Gln Ile Leu Glu Glu Asn Val Glu Val 2040 2045 2050	6258
gaa atc tgg aca aaa gaa ggg gaa agg aag aaa ttg aaa ccc aga tgg Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp 2055 2060 2065 2070	6306
ttg gat gct agg atc tat tct gac cca ctg cgc cta aaa gaa ttt aag Leu Asp Ala Arg Ile Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys 2075 2080 2085	6354
gaa ttt gca gcc gga aga aag tct ctg acc ctg aac cta atc aca gaa Glu Phe Ala Ala Gly Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu 2090 2095 2100	6402
atg ggt agg ctc cca acc ttc atg act cag aag gca aga gac gca ctg Met Gly Arg Leu Pro Thr Phe Met Thr Gln Lys Ala Arg Asp Ala Leu 2105 2110 2115	6450
gac aac tta gca gtg ctg cac acg gct gag gca ggt gga agg cgc tac Asp Asn Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala Tyr 2120 2125 2130	6498
aac cat gct ctc agt gaa ctg ccg gag acc ctg gag aca ttg ctt tta Asn His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu Leu Leu 2135 2140 2145 2150	6546

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ctg aca ctt ctg gct aca gtc acg gga ggg atc ttt tta ttc ttg atg	6594
Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu Phe Leu Met	
2155 2160 2165	
agc gca agg ggc ata ggg aag atg acc ctg gga atg tgc tgc ata atc	6642
Ser Ala Arg Gly Ile Gly Lys Met Thr Leu Gly Met Cys Cys Ile Ile	
2170 2175 2180	
acg gct agc atc ctc cta tgg tac gca caa ata cag cca cac tgg ata	6690
Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln Ile Gln Pro His Trp Ile	
2185 2190 2195	
gca gct tca ata ata ctg gag ttt ttt ctc ata gtt ttg ctt att cca	6738
Ala Ala Ser Ile Ile Leu Leu Phe Phe Leu Ile Val Leu Leu Ile Pro	
2200 2205 2210	
gaa cct gaa aaa cag aga aca ccc caa gac aac caa ctg acc tac gtt	6786
Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn Gln Leu Thr Tyr Val	
2215 2220 2225 2230	
gtc ata gcc atc ctc aca gtg gtg gcc gca acc atg gca aac gag atg	6834
Val Ile Ala Ile Leu Thr Val Val Ala Ala Thr Met Ala Asn Glu Met	
2235 2240 2245	
ggt ttc cta gaa aaa acg aag aaa gat ctc gga ttg gga agc att gca	6882
Gly Phe Leu Glu Lys Thr Lys Lys Asp Leu Gly Leu Gly Ser Ile Ala	
2250 2255 2260	
acc cag caa ccc gag agc aac atc ctg gac ata gat cta cgt cct gca	6930
Thr Gln Gln Pro Glu Ser Asn Ile Leu Asp Ile Asp Leu Arg Pro Ala	
2265 2270 2275	
tca gca tgg acg ctg tat gcc gtg gcc aca aca ttt gtt aca cca atg	6978
Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Phe Val Thr Pro Met	
2280 2285 2290	
ttg aga cat agc att gaa aat tcc tca gtg aat gtg tcc cta aca gct	7026
Leu Arg His Ser Ile Glu Asn Ser Ser Val Asn Val Ser Leu Thr Ala	
2295 2300 2305 2310	
ata gcc aac caa gcc aca gtg tta atg ggt ctc ggg aaa gga tgg cca	7074
Ile Ala Asn Gln Ala Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro	
2315 2320 2325	
ttg tca aag atg gac atc gga gtt ccc ctt ctc gcc att gga tgc tac	7122
Leu Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala Ile Gly Cys Tyr	
2330 2335 2340	
tca caa gtc aac ccc ata act ctc aca gca gct ctt ttc tta ttg gta	7170
Ser Gln Val Asn Pro Ile Thr Leu Thr Ala Ala Leu Phe Leu Leu Val	
2345 2350 2355	
gca cat tat gcc atc ata ggg cca gga ctc caa gca aaa gca acc aga	7218
Ala His Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg	
2360 2365 2370	

gaa gct cag aaa aga gca gcg gcg ggc atc atg aaa aac cca act gtc Glu Ala Gln Lys Arg Ala Ala Ala Gly Ile Met Lys Asn Pro Thr Val 2375 2380 2385 2390	7266
gat gga ata aca gtg att gac cta gat cca ata cct tat gat cca aag Asp Gly Ile Thr Val Ile Asp Leu Asp Pro Ile Pro Tyr Asp Pro Lys 2395 2400 2405	7314
ttt gaa aag cag ttg gga caa gta atg ctc cta gtc ctc tgc gtg act Phe Glu Lys Gln Leu Gly Gln Val Met Leu Leu Val Leu Cys Val Thr 2410 2415 2420	7362
caa gta ttg atg atg agg act aca tgg gct ctg tgt gag gct tta acc Gln Val Leu Met Met Arg Thr Thr Trp Ala Leu Cys Glu Ala Leu Thr 2425 2430 2435	7410
tta gct acc ggg ccc atc tcc aca ttg tgg gaa gga aat cca ggg agg Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp Glu Gly Asn Pro Gly Arg 2440 2445 2450	7458
ttt tgg aac act acc att gcg gtg tca atg gct aac att ttt aga ggg Phe Trp Asn Thr Thr Ile Ala Val Ser Met Ala Asn Ile Phe Arg Gly 2455 2460 2465 2470	7506
agt tac ttg gcc gga gct gga ctt ctc ttt tot att atg aag aac aca Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe Ser Ile Met Lys Asn Thr 2475 2480 2485	7554
acc aac aca aga agg gga act ggc aac ata gga gag acg ctt gga gag Thr Asn Thr Arg Arg Gly Thr Gly Asn Ile Gly Glu Thr Leu Gly Glu 2490 2495 2500	7602
aaa tgg aaa agc cga ttg aac gca ttg gga aaa agt gaa ttc cag atc Lys Trp Lys Ser Arg Leu Asn Ala Leu Gly Lys Ser Glu Phe Gln Ile 2505 2510 2515	7650
tac aag aaa agt gga atc cag gaa gtg gat aga acc tta gca aaa gaa Tyr Lys Lys Ser Gly Ile Gln Glu Val Asp Arg Thr Leu Ala Lys Glu 2520 2525 2530	7698
ggc att aaa aga gga gaa acg gac cat cac gct gtg tgc cga ggc tca Gly Ile Lys Arg Gly Glu Thr Asp His His Ala Val Ser Arg Gly Ser 2535 2540 2545 2550	7746
gca aaa ctg aga tgg ttc gtt gag aga aac atg gtc aca cca gaa ggg Ala Lys Leu Arg Trp Phe Val Glu Arg Asn Met Val Thr Pro Glu Gly 2555 2560 2565	7794
aaa gta gtg gac ctc ggt tgt ggc aga gga ggc tgg tca tac tat tgt Lys Val Val Asp Leu Gly Cys Gly Arg Gly Gly Trp Ser Tyr Tyr Cys 2570 2575 2580	7842

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gga gga cta aag aat gta aga gaa gtc aaa ggc cta aca aaa gga gga Gly Gly Leu Lys Asn Val Arg Glu Val Lys Gly Leu Thr Lys Gly Gly 2585 2590 2595	7890
cca gga cac gaa gaa ccc atc ccc atg tca aca tat ggg tgg aat cta Pro Gly His Glu Glu Pro Ile Pro Met Ser Thr Tyr Gly Trp Asn Leu 2600 2605 2610	7938
gtg cgt ctt caa agt gga gtt gac gtt ttc ttc atc ccg cca gaa aag Val Arg Leu Gln Ser Gly Val Asp Val Phe Phe Ile Pro Pro Glu Lys 2615 2620 2625 2630	7986
tgt gac aca tta ttg tgt gac ata ggg gag tca tca cca aat ccc aca Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro Thr 2635 2640 2645	8034
gtg gaa gca gga cga aca ctc aga gtc ctt aac tta gta gaa aat tgg Val Glu Ala Gly Arg Thr Leu Arg Val Leu Asn Leu Val Glu Asn Trp 2650 2655 2660	8082
ttg aac aac aac act caa ttt tgc ata aag gtt ctc aac cca tat atg Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys Val Leu Asn Pro Tyr Met 2665 2670 2675	8130
ccc tca gtc ata gaa aaa atg gaa gca cta caa agg aaa tat gga gga Pro Ser Val Ile Glu Lys Met Glu Ala Leu Gln Arg Lys Tyr Gly Gly 2680 2685 2690	8178
gcc tta gtg agg aat cca ctc tca cga aac tcc aca cat gag atg tac Ala Leu Val Arg Asn Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr 2695 2700 2705 2710	8226
tgg gta tcc aat gct tcc ggg aac ata gtg tca tca gtg aac atg att Trp Val Ser Asn Ala Ser Gly Asn Ile Val Ser Ser Val Asn Met Ile 2715 2720 2725	8274
tca agg atg ttg atc aac aga ttt aca atg aga tac aag aaa gcc act Ser Arg Met Leu Ile Asn Arg Phe Thr Met Arg Tyr Lys Lys Ala Thr 2730 2735 2740	8322
tac gag ccg gat gtt gac ctc gga agc gga acc cgt aac atc ggg att Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly Thr Arg Asn Ile Gly Ile 2745 2750 2755	8370
gaa agt gag ata cca aac cta gat ata att ggg aaa aga ata gaa aaa Glu Ser Glu Ile Pro Asn Leu Asp Ile Ile Gly Lys Arg Ile Glu Lys 2760 2765 2770	8418
ata aag caa gag cat gaa aca tca tgg cac tat gac caa gac cac cca Ile Lys Gln Glu His Glu Thr Ser Trp His Tyr Asp Gln Asp His Pro 2775 2780 2785 2790	8466
tac aaa acg tgg gca tac cat ggt agc tat gaa aca aaa cag act gga Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly 2795 2800 2805	8514

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tca gca tca tcc atg gtc aac gga gtg gtc agg ctg ctg aca aaa cct Ser Ala Ser Ser Met Val Asn Gly Val Val Arg Leu Thr Lys Pro 2810 2815 2820	8562
tgg gac gtc gtc ccc atg gtg aca cag atg gca atg aca gac acg act Trp Asp Val Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr 2825 2830 2835	8610
cca ttt gga caa cag cgc gtt ttt aaa gag aaa gtg gac acg aga acc Pro Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr 2840 2845 2850	8658
caa gaa ccg aaa gaa ggc acg aag aaa cta atg aaa ata aca gca gag Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu Met Lys Ile Thr Ala Glu 2855 2860 2865 2870	8706
tgg ctt tgg aaa gaa tta ggg aag aaa aag aca ccc agg atg tgc acc Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys Thr Pro Arg Met Cys Thr 2875 2880 2885	8754
aga gaa gaa ttc aca aga aag gtg aga agc aat gca gcc ttg ggg gcc Arg Glu Glu Phe Thr Arg Lys Val Arg Ser Asn Ala Ala Leu Gly Ala 2890 2895 2900	8802
ata ttc act gat gag aac aag tgg aag tcg gca cgt gag gct gtt gaa Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser Ala Arg Glu Ala Val Glu 2905 2910 2915	8850
gat agt agg ttt tgg gag ctg gtt gac aag gaa agg aat ctc cat ctt Asp Ser Arg Phe Trp Glu Leu Val Asp Lys Glu Arg Asn Leu His Leu 2920 2925 2930	8898
gaa gga aag tgt gaa aca tgt gtg tac aac atg atg gga aaa aga gag Glu Gly Lys Cys Glu Thr Cys Val Tyr Asn Met Met Gly Lys Arg Glu 2935 2940 2945 2950	8946
aag aag cta ggg gaa ttc ggc aag gca aaa ggc agc aga gcc ata tgg Lys Lys Leu Gly Glu Phe Gly Lys Ala Lys Gly Ser Arg Ala Ile Trp 2955 2960 2965	8994
tac atg tgg ctt gga gca cgc ttc tta gag ttt gaa gcc cta gga ttc Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu Phe Glu Ala Leu Gly Phe 2970 2975 2980	9042
tta aat gaa gat cac tgg ttc tcc aga gag aac tcc ctg agt gga gtg Leu Asn Glu Asp His Trp Phe Ser Arg Glu Asn Ser Leu Ser Gly Val 2985 2990 2995	9090
gaa gga gaa ggg ctg cac aag cta ggt tac att cta aga gac gtg agc Glu Gly Glu Gly Leu His Lys Leu Gly Tyr Ile Leu Arg Asp Val Ser 3000 3005 3010	9138

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aag aaa gag gga gga gca atg tat gcc gat gac acc gca gga tgg gat Lys Lys Glu Gly Gly Ala Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp 3015 3020 3025 3030	9186
aca aga atc aca cta gaa gac cta aaa aat gaa gaa atg gta aca aac Thr Arg Ile Thr Leu Glu Asp Leu Lys Asn Glu Met Val Thr Asn 3035 3040 3045	9234
cac atg gaa gga gaa cac aag aaa cta gcc gag gcc att ttc aaa cta His Met Glu Gly Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu 3050 3055 3060	9282
acg tac caa aac aag gtg gtg cgt gtg caa aga cca aca cca aga ggc Thr Tyr Gln Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly 3065 3070 3075	9330
aca gta atg gac atc ata tcg aga aga gac caa aga ggt agt gga caa Thr Val Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly Gln 3080 3085 3090	9378
gtt ggc acc tat gga ctc aat act ttc acc aat atg gaa gcc caa cta Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu 3095 3100 3105 3110	9426
atc aga cag atg gag gga gaa gga gtc ttt aaa agc att cag cac cta Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile Gln His Leu 3115 3120 3125	9474
aca atc aca gaa gaa atc gct gtg caa aac tgg tta gca aga gtg ggg Thr Ile Thr Glu Glu Ile Ala Val Gln Asn Trp Leu Ala Arg Val Gly 3130 3135 3140	9522
cgc gaa agg tta tca aga atg gcc atc agt gga gat gat tgt gtt gtg Arg Glu Arg Leu Ser Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val 3145 3150 3155	9570
aaa cct tta gat gac agg ttc gca agc gct tta aca gct cta aat gac Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala Leu Thr Ala Leu Asn Asp 3160 3165 3170	9618
atg gga aag att agg aaa gac ata caa caa tgg gaa cct tca aga gga Met Gly Lys Ile Arg Lys Asp Ile Gln Gln Trp Glu Pro Ser Arg Gly 3175 3180 3185 3190	9666
tgg aat gat tgg aca caa gtg ccc ttc tgt tca cac cat ttc cat gag Trp Asn Asp Trp Thr Gln Val Pro Phe Cys Ser His His Phe His Glu 3195 3200 3205	9714
tta atc atg aaa gac ggt cgc gta ctc gtt gtt cca tgt aga aac caa Leu Ile Met Lys Asp Gly Arg Val Leu Val Val Pro Cys Arg Asn Gln 3210 3215 3220	9762
gat gaa ctg att ggc aga gcc cga atc tcc caa gga gca ggg tgg tct Asp Glu Leu Ile Gly Arg Ala Arg Ile Ser Gln Gly Ala Gly Trp Ser 3225 3230 3235	9810

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ttg cgg gag acg gcc tgt	ttg ggg aag tct tac gcc caa atg tgg agc	9858
Leu Arg Glu Thr Ala Cys	Leu Gly Lys Ser Tyr Ala Gln Met Trp Ser	
3240	3245 3250	
ttg atg tac ttc cac aga cgc gac ctc agg	ctg gcg gca aat gct att	9906
Leu Met Tyr Phe His Arg Arg Asp Leu Arg	Leu Ala Ala Asn Ala Ile	
3255	3260 3265 3270	
tgc tgc gca gta cca tca cat tgg gtt cca	aca agt cga aca acc tgg	9954
Cys Ser Ala Val Pro Ser His Trp Val Pro	Thr Ser Arg Thr Trp Trp	
3275	3280 3285	
tcc ata cat gct aaa cat gaa tgg atg aca	acg gaa gac atg ctg aca	10002
Ser Ile His Ala Lys His Glu Trp Met Thr	Thr Glu Asp Met Leu Thr	
3290	3295 3300	
gtc tgg aac agg gtg tgg att caa gaa aac	cca tgg atg gaa gac aaa	10050
Val Trp Asn Arg Val Trp Ile Gln Glu Asn	Pro Trp Met Glu Asp Lys	
3305	3310 3315	
act cca gtg gaa tca tgg gag gaa atc cca	tac ttg ggg aaa aga gaa	10098
Thr Pro Val Glu Ser Trp Glu Glu Ile Pro	Tyr Leu Gly Lys Arg Glu	
3320	3325 3330	
gac caa tgg tgc ggc tca ttg att ggg tta	aca agc agg gcc acc tgg	10146
Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu	Thr Ser Arg Ala Thr Trp	
3335	3340 3345 3350	
gca aag aac atc caa gca gca ata aat caa	gtt aga tcc ctt ata ggc	10194
Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln	Val Arg Ser Leu Ile Gly	
3355	3360 3365	
aat gaa gaa tac aca gat tac atg cca tcc	atg aaa aga ttc aga aga	10242
Asn Glu Glu Tyr Thr Asp Tyr Met Pro Ser	Met Lys Arg Phe Arg Arg	
3370	3375 3380	
gaa gag gaa gaa gca gga gtt ctg tgg tag	aaagcaaaac taacatgaaa	10292
Glu Glu Glu Glu Ala Gly Val Leu Trp *		
3385	3390	
caaggctaga agtcaggctg gattaagcca tagtacggaa	aaaactatgc tacctgtgag	10352
ccccgtccaa ggacgttaaa agaagtcagg ccatcataaa	tgccatagct tgagtaaaact	10412
atgcagcctg tagctccacc tgagaaggtg taataaaatcc	gggaggccac aaaccatgga	10472
agctgtacgc atggcgtagt ggactagcgg ttagaggaga	ccctccctctt acaaatcgca	10532
gcaacaatgg gggcccaagg cgagatgaag ctgtagctc	gctggaagga ctagagggtta	10592
gaggagacc ccccgaaaca aaaaacagca tattgacgct	gggaaagacc agagatcctg	10652
ctgtctcctc agcatcattc caggcagaca acgccagaaa	atggaatggt gctgttgaat	10712
caacaggttc t		10723

<210> 12

<211> 3391

<212> PRT

<213> Artificial Sequence

139

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<400> 12

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Met Asn Asn Gln Arg Lys Lys Ala Lys Asn Thr Pro Phe Asn Met Leu
 1           5           10           15
Lys Arg Glu Arg Asn Arg Val Ser Thr Val Gln Gln Leu Thr Lys Arg
      20           25           30
Phe Ser Leu Gly Met Leu Gln Gly Arg Gly Pro Leu Lys Leu Phe Met
      35           40           45
Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly
      50           55           60
Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val
 65           70           75           80
Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn
      85           90           95
Arg Arg Arg Ser Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val
      100          105          110
Met Ala Phe His Leu Thr Thr Arg Asp Gly Glu Pro Leu Met Ile Val
      115          120          125
Ala Lys His Glu Arg Gly Arg Pro Leu Leu Phe Lys Thr Thr Glu Gly
      130          135          140
Ile Asn Lys Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Met Cys Glu
 145          150          155          160
Asp Thr Val Thr Tyr Lys Cys Pro Leu Leu Val Asn Thr Glu Pro Glu
      165          170          175
Asp Ile Asp Cys Trp Cys Asn Leu Thr Ser Thr Trp Val Met Tyr Gly
      180          185          190
Thr Cys Thr Gln Ser Gly Glu Arg Arg Arg Glu Lys Arg Ser Val Ala
      195          200          205
Leu Thr Pro His Ser Gly Met Gly Leu Glu Thr Arg Ala Glu Thr Trp
      210          215          220
Met Ser Ser Glu Gly Ala Trp Lys His Ala Gln Arg Val Glu Ser Trp
 225          230          235          240
Ile Leu Arg Asn Pro Gly Phe Ala Leu Leu Ala Gly Phe Met Ala Tyr
      245          250          255
Met Ile Gly Gln Thr Gly Ile Gln Arg Thr Val Phe Phe Val Leu Met
      260          265          270
Met Leu Val Ala Pro Ser Tyr Gly Met Arg Cys Val Gly Val Gly Asn
      275          280          285
Arg Asp Phe Val Glu Gly Val Ser Gly Gly Ala Trp Val Asp Leu Val
      290          295          300
Leu Glu His Gly Gly Cys Val Thr Thr Met Ala Gln Gly Lys Pro Thr
 305          310          315          320
Leu Asp Phe Glu Leu Thr Lys Thr Thr Ala Lys Glu Val Ala Leu Leu
      325          330          335
Arg Thr Tyr Cys Ile Glu Ala Ser Ile Ser Asn Ile Thr Thr Ala Thr
      340          345          350
Arg Cys Pro Thr Gln Gly Glu Pro Tyr Leu Lys Glu Glu Gln Asp Gln
      355          360          365
Gln Tyr Ile Cys Arg Arg Asp Val Val Asp Arg Gly Trp Gly Asn Gly
      370          375          380

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140

Cys	Gly	Leu	Phe	Gly	Lys	Gly	Gly	Val	Val	Thr	Cys	Ala	Lys	Phe	Ser		
385					390					395					400		
Cys	Ser	Gly	Lys	Ile	Thr	Gly	Asn	Leu	Val	Gln	Ile	Glu	Asn	Leu	Glu		
				405						410					415		
Tyr	Thr	Val	Val	Val	Thr	Val	His	Asn	Gly	Asp	Thr	His	Ala	Val	Gly		
				420				425					430				
Asn	Asp	Thr	Ser	Asn	His	Gly	Val	Thr	Ala	Thr	Ile	Thr	Pro	Arg	Ser		
		435				440						445					
Pro	Ser	Val	Glu	Val	Lys	Leu	Pro	Asp	Tyr	Gly	Glu	Leu	Thr	Leu	Asp		
		450				455				460							
Cys	Glu	Pro	Arg	Ser	Gly	Ile	Asp	Phe	Asn	Glu	Met	Ile	Leu	Met	Lys		
465				470						475					480		
Met	Lys	Lys	Lys	Thr	Trp	Leu	Val	His	Lys	Gln	Trp	Phe	Leu	Asp	Leu		
				485				490						495			
Pro	Leu	Pro	Trp	Thr	Ala	Gly	Ala	Asp	Thr	Ser	Glu	Val	His	Trp	Asn		
			500					505					510				
Tyr	Lys	Glu	Arg	Met	Val	Thr	Phe	Lys	Val	Pro	His	Ala	Lys	Arg	Gln		
		515				520						525					
Asp	Val	Thr	Val	Leu	Gly	Ser	Gln	Glu	Gly	Ala	Met	His	Ser	Ala	Leu		
		530				535					540						
Ala	Gly	Ala	Thr	Glu	Val	Asp	Ser	Gly	Asp	Gly	Asn	His	Met	Phe	Ala		
545				550						555					560		
Gly	His	Leu	Lys	Cys	Lys	Val	Arg	Met	Glu	Lys	Leu	Arg	Ile	Lys	Gly		
				565				570						575			
Met	Ser	Tyr	Thr	Met	Cys	Ser	Gly	Lys	Phe	Ser	Ile	Asp	Lys	Glu	Met		
			580					585					590				
Ala	Glu	Thr	Gln	His	Gly	Thr	Thr	Val	Val	Lys	Val	Lys	Tyr	Glu	Gly		
		595				600						605					
Ala	Gly	Ala	Pro	Cys	Lys	Val	Pro	Ile	Glu	Ile	Arg	Asp	Val	Asn	Lys		
		610				615					620						
Glu	Lys	Val	Val	Gly	Arg	Ile	Ile	Ser	Ser	Thr	Pro	Leu	Ala	Glu	Asn		
625				630						635				640			
Thr	Asn	Ser	Val	Thr	Asn	Ile	Glu	Leu	Glu	Pro	Pro	Phe	Gly	Asp	Ser		
				645					650					655			
Tyr	Ile	Val	Ile	Gly	Val	Gly	Asn	Ser	Ala	Leu	Thr	Leu	His	Trp	Phe		
			660				665						670				
Arg	Lys	Gly	Ser	Ser	Ile	Gly	Lys	Met	Phe	Glu	Ser	Thr	Tyr	Arg	Gly		
		675					680						685				
Ala	Lys	Arg	Met	Ala	Ile	Leu	Gly	Glu	Thr	Ala	Trp	Asp	Phe	Gly	Ser		
			690			695					700						
Val	Gly	Gly	Leu	Phe	Thr	Ser	Leu	Gly	Lys	Ala	Val	His	Gln	Val	Phe		
705				710						715					720		
Gly	Ser	Val	Tyr	Thr	Thr	Leu	Phe	Gly	Gly	Val	Ser	Trp	Met	Ile	Arg		
				725					730					735			
Ile	Leu	Ile	Gly	Phe	Leu	Val	Leu	Trp	Ile	Gly	Thr	Asn	Ser	Arg	Asn		
			740					745					750				
Thr	Ser	Met	Ala	Met	Thr	Cys	Ile	Ala	Ala	Gly	Ile	Val	Thr	Leu	Tyr		
		755				760						765					
Leu	Gly	Val	Met	Val	Gln	Ala	Asp	Ser	Gly	Cys	Val	Val	Ser	Trp	Lys		
		770				775					780						
Asn	Lys	Glu	Leu	Lys	Cys	Gly	Ser	Gly	Ile	Phe	Ile	Thr	Asp	Asn	Val		
785				790						795					800		
His	Thr	Trp	Thr	Glu	Gln	Tyr	Lys	Phe	Gln	Pro	Glu	Ser	Pro	Ser	Lys		
				805						810					815		

141

Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile
 820 825 830
 Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro
 835 840 845
 Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met
 850 855 860
 Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg
 865 870 875 880
 Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala
 885 890 895
 Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly
 900 905 910
 Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu
 915 920 925
 Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu
 930 935 940
 Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser
 945 950 955 960
 Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp
 965 970 975
 Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe
 980 985 990
 Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser
 995 1000 1005
 Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala Gly
 1010 1015 1020
 Pro Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr
 1025 1030 1035 1040
 Gly Pro Trp His Leu Gly Lys Leu Glu Met Asp Phe Asp Phe Cys Asp
 1045 1050 1055
 Gly Thr Thr Val Val Val Thr Glu Asp Cys Gly Asn Arg Gly Pro Ser
 1060 1065 1070
 Leu Arg Thr Thr Thr Ala Ser Gly Lys Leu Ile Thr Glu Trp Cys Cys
 1075 1080 1085
 Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr Arg Gly Glu Asp Gly Cys
 1090 1095 1100
 Trp Tyr Gly Met Glu Ile Arg Pro Leu Lys Glu Lys Glu Glu Asn Leu
 1105 1110 1115 1120
 Val Asn Ser Leu Val Thr Ala Gly His Gly Gln Val Asp Asn Phe Ser
 1125 1130 1135
 Leu Gly Val Leu Gly Met Ala Leu Phe Leu Glu Glu Met Leu Arg Thr
 1140 1145 1150
 Arg Val Gly Thr Lys His Ala Ile Leu Leu Val Ala Val Ser Phe Val
 1155 1160 1165
 Thr Leu Ile Thr Gly Asn Met Ser Phe Arg Asp Leu Gly Arg Val Met
 1170 1175 1180
 Val Met Val Gly Ala Thr Met Thr Asp Asp Ile Gly Met Gly Val Thr
 1185 1190 1195 1200
 Tyr Leu Ala Leu Leu Ala Ala Phe Lys Val Arg Pro Thr Phe Ala Ala
 1205 1210 1215
 Gly Leu Leu Leu Arg Lys Leu Thr Ser Lys Glu Leu Met Met Thr Thr
 1220 1225 1230
 Ile Gly Ile Val Leu Leu Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu
 1235 1240 1245

142

Glu Leu Thr Asp Ala Leu Ala Leu Gly Met Met Val Leu Lys Met Val
 1250 1255 1260
 Arg Asn Met Glu Lys Tyr Gln Leu Ala Val Thr Ile Met Ala Ile Leu
 1265 1270 1275 1280
 Cys Val Pro Asn Ala Val Ile Leu Gln Asn Ala Trp Lys Val Ser Cys
 1285 1290 1295
 Thr Ile Leu Ala Val Val Ser Val Ser Pro Leu Phe Leu Thr Ser Ser
 1300 1305 1310
 Gln Gln Lys Thr Asp Trp Ile Pro Leu Ala Leu Thr Ile Lys Gly Leu
 1315 1320 1325
 Asn Pro Thr Ala Ile Phe Leu Thr Thr Leu Ser Arg Thr Ser Lys Lys
 1330 1335 1340
 Arg Ser Trp Pro Leu Asn Glu Ala Ile Met Ala Val Gly Met Val Ser
 1345 1350 1355 1360
 Ile Leu Ala Ser Ser Leu Leu Lys Asn Asp Ile Pro Met Thr Gly Pro
 1365 1370 1375
 Leu Val Ala Gly Gly Leu Leu Thr Val Cys Tyr Val Leu Thr Gly Arg
 1380 1385 1390
 Ser Ala Asp Leu Glu Leu Glu Arg Ala Ala Asp Val Lys Trp Glu Asp
 1395 1400 1405
 Gln Ala Glu Ile Ser Gly Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser
 1410 1415 1420
 Glu Asp Gly Ser Met Ser Ile Lys Asn Glu Glu Glu Glu Thr Leu
 1425 1430 1435 1440
 Thr Ile Leu Ile Arg Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro
 1445 1450 1455
 Val Ser Ile Pro Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys
 1460 1465 1470
 Lys Gln Arg Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Met
 1475 1480 1485
 Gly Lys Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys Gly
 1490 1495 1500
 Ile Leu Gly Tyr Ser Gln Ile Gly Ala Gly Val Tyr Lys Glu Gly Thr
 1505 1510 1515 1520
 Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu Met His Lys
 1525 1530 1535
 Gly Lys Arg Ile Glu Pro Ser Trp Ala Asp Val Lys Lys Asp Leu Ile
 1540 1545 1550
 Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu Trp Lys Glu Gly Glu
 1555 1560 1565
 Glu Val Gln Val Leu Ala Leu Glu Pro Gly Lys Asn Pro Arg Ala Val
 1570 1575 1580
 Gln Thr Lys Pro Gly Leu Phe Lys Thr Asn Ala Gly Thr Ile Gly Ala
 1585 1590 1595 1600
 Val Ser Leu Asp Phe Ser Pro Gly Thr Ser Gly Ser Pro Ile Ile Asp
 1605 1610 1615
 Lys Lys Gly Lys Val Val Gly Leu Tyr Gly Asn Gly Val Val Thr Arg
 1620 1625 1630
 Ser Gly Ala Tyr Val Ser Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu
 1635 1640 1645
 Asp Asn Pro Glu Ile Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr
 1650 1655 1660
 Ile Met Asp Leu His Pro Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro
 1665 1670 1675 1680

143

Ala Ile Val Arg Glu Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu
 1685 1690 1695
 Ala Pro Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly
 1700 1705 1710
 Leu Pro Ile Arg Tyr Gln Thr Pro Ala Ile Arg Ala Val His Thr Gly
 1715 1720 1725
 Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg Leu
 1730 1735 1740
 Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu
 1745 1750 1755 1760
 Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser
 1765 1770 1775
 Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe Met Thr Ala Thr
 1780 1785 1790
 Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser Asn Ala Pro Ile Ile
 1795 1800 1805
 Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser Trp Asn Ser Gly His Glu
 1810 1815 1820
 Trp Val Thr Asp Phe Lys Gly Lys Thr Val Trp Phe Val Pro Ser Ile
 1825 1830 1835 1840
 Lys Ala Gly Asn Asp Ile Ala Ala Cys Leu Arg Lys Asn Gly Lys Lys
 1845 1850 1855
 Val Ile Gln Leu Ser Arg Lys Thr Phe Asp Ser Glu Tyr Val Lys Thr
 1860 1865 1870
 Arg Thr Asn Asp Trp Asp Phe Val Val Thr Thr Asp Ile Ser Glu Met
 1875 1880 1885
 Gly Ala Asn Phe Lys Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met
 1890 1895 1900
 Lys Pro Val Ile Leu Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly
 1905 1910 1915 1920
 Pro Met Pro Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile
 1925 1930 1935
 Gly Arg Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu
 1940 1945 1950
 Pro Leu Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met
 1955 1960 1965
 Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met Phe
 1970 1975 1980
 Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu
 1985 1990 1995 2000
 Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg Arg Gly Asp
 2005 2010 2015
 Leu Pro Val Trp Leu Ala Tyr Arg Val Ala Ala Glu Gly Ile Asn Tyr
 2020 2025 2030
 Ala Asp Arg Arg Trp Cys Phe Asp Gly Val Lys Asn Asn Gln Ile Leu
 2035 2040 2045
 Glu Glu Asn Val Glu Val Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys
 2050 2055 2060
 Lys Leu Lys Pro Arg Trp Leu Asp Ala Arg Ile Tyr Ser Asp Pro Leu
 2065 2070 2075 2080
 Ala Leu Lys Glu Phe Lys Glu Phe Ala Ala Gly Arg Lys Ser Leu Thr
 2085 2090 2095
 Leu Asn Leu Ile Thr Glu Met Gly Arg Leu Pro Thr Phe Met Thr Gln
 2100 2105 2110

144

Lys Ala Arg Asp Ala Leu Asp Asn Leu Ala Val Leu His Thr Ala Glu
 2115 2120 2125
 Ala Gly Gly Arg Ala Tyr Asn His Ala Leu Ser Glu Leu Pro Glu Thr
 2130 2135 2140
 Leu Glu Thr Leu Leu Leu Thr Leu Leu Ala Thr Val Thr Gly Gly
 2145 2150 2155 2160
 Ile Phe Leu Phe Leu Met Ser Ala Arg Gly Ile Gly Lys Met Thr Leu
 2165 2170 2175
 Gly Met Cys Cys Ile Ile Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln
 2180 2185 2190
 Ile Gln Pro His Trp Ile Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu
 2195 2200 2205
 Ile Val Leu Leu Ile Pro Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp
 2210 2215 2220
 Asn Gln Leu Thr Tyr Val Val Ile Ala Ile Leu Thr Val Val Ala Ala
 2225 2230 2235 2240
 Thr Met Ala Asn Glu Met Gly Phe Leu Glu Lys Thr Lys Lys Asp Leu
 2245 2250 2255
 Gly Leu Gly Ser Ile Ala Thr Gln Gln Pro Glu Ser Asn Ile Leu Asp
 2260 2265 2270
 Ile Asp Leu Arg Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr
 2275 2280 2285
 Thr Phe Val Thr Pro Met Leu Arg His Ser Ile Glu Asn Ser Ser Val
 2290 2295 2300
 Asn Val Ser Leu Thr Ala Ile Ala Asn Gln Ala Thr Val Leu Met Gly
 2305 2310 2315 2320
 Leu Gly Lys Gly Trp Pro Leu Ser Lys Met Asp Ile Gly Val Pro Leu
 2325 2330 2335
 Leu Ala Ile Gly Cys Tyr Ser Gln Val Asn Pro Ile Thr Leu Thr Ala
 2340 2345 2350
 Ala Leu Phe Leu Leu Val Ala His Tyr Ala Ile Ile Gly Pro Gly Leu
 2355 2360 2365
 Gln Ala Lys Ala Thr Arg Glu Ala Gln Lys Arg Ala Ala Ala Gly Ile
 2370 2375 2380
 Met Lys Asn Pro Thr Val Asp Gly Ile Thr Val Ile Asp Leu Asp Pro
 2385 2390 2395 2400
 Ile Pro Tyr Asp Pro Lys Phe Glu Lys Gln Leu Gly Gln Val Met Leu
 2405 2410 2415
 Leu Val Leu Cys Val Thr Gln Val Leu Met Met Arg Thr Thr Trp Ala
 2420 2425 2430
 Leu Cys Glu Ala Leu Thr Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp
 2435 2440 2445
 Glu Gly Asn Pro Gly Arg Phe Trp Asn Thr Thr Ile Ala Val Ser Met
 2450 2455 2460
 Ala Asn Ile Phe Arg Gly Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe
 2465 2470 2475 2480
 Ser Ile Met Lys Asn Thr Thr Asn Thr Arg Arg Gly Thr Gly Asn Ile
 2485 2490 2495
 Gly Glu Thr Leu Gly Glu Lys Trp Lys Ser Arg Leu Asn Ala Leu Gly
 2500 2505 2510
 Lys Ser Glu Phe Gln Ile Tyr Lys Lys Ser Gly Ile Gln Glu Val Asp
 2515 2520 2525
 Arg Thr Leu Ala Lys Glu Gly Ile Lys Arg Gly Glu Thr Asp His His
 2530 2535 2540

145

Ala Val Ser Arg Gly Ser Ala Lys Leu Arg Trp Phe Val Glu Arg Asn
 2545 2550 2555 2560
 Met Val Thr Pro Glu Gly Lys Val Val Asp Leu Gly Cys Gly Arg Gly
 2565 2570 2575
 Gly Trp Ser Tyr Trp Cys Gly Gly Leu Lys Asn Val Arg Glu Val Lys
 2580 2585 2590
 Gly Leu Thr Lys Gly Gly Pro Gly His Glu Glu Pro Ile Pro Met Ser
 2595 2600 2605
 Thr Tyr Gly Trp Asn Leu Val Arg Leu Gln Ser Gly Val Asp Val Phe
 2610 2615 2620
 Phe Ile Pro Pro Glu Lys Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu
 2625 2630 2635 2640
 Ser Ser Pro Asn Pro Thr Val Glu Ala Gly Arg Thr Leu Arg Val Leu
 2645 2650 2655
 Asn Leu Val Glu Asn Trp Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys
 2660 2665 2670
 Val Leu Asn Pro Tyr Met Pro Ser Val Ile Glu Lys Met Glu Ala Leu
 2675 2680 2685
 Gln Arg Lys Tyr Gly Gly Ala Leu Val Arg Asn Pro Leu Ser Arg Asn
 2690 2695 2700
 Ser Thr His Glu Met Tyr Trp Val Ser Asn Ala Ser Gly Asn Ile Val
 2705 2710 2715 2720
 Ser Ser Val Asn Met Ile Ser Arg Met Leu Ile Asn Arg Phe Thr Met
 2725 2730 2735
 Arg Tyr Lys Lys Ala Thr Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly
 2740 2745 2750
 Thr Arg Asn Ile Gly Ile Glu Ser Glu Ile Pro Asn Leu Asp Ile Ile
 2755 2760 2765
 Gly Lys Arg Ile Glu Lys Ile Lys Gln Glu His Glu Thr Ser Trp His
 2770 2775 2780
 Tyr Asp Gln Asp His Pro Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr
 2785 2790 2795 2800
 Glu Thr Lys Gln Thr Gly Ser Ala Ser Ser Met Val Asn Gly Val Val
 2805 2810 2815
 Arg Leu Leu Thr Lys Pro Trp Asp Val Val Pro Met Val Thr Gln Met
 2820 2825 2830
 Ala Met Thr Asp Thr Thr Pro Phe Gly Gln Gln Arg Val Phe Lys Glu
 2835 2840 2845
 Lys Val Asp Thr Arg Thr Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu
 2850 2855 2860
 Met Lys Ile Thr Ala Glu Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys
 2865 2870 2875 2880
 Thr Pro Arg Met Cys Thr Arg Glu Glu Phe Thr Arg Lys Val Arg Ser
 2885 2890 2895
 Asn Ala Ala Leu Gly Ala Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser
 2900 2905 2910
 Ala Arg Glu Ala Val Glu Asp Ser Arg Phe Trp Glu Leu Val Asp Lys
 2915 2920 2925
 Glu Arg Asn Leu His Leu Glu Gly Lys Cys Glu Thr Cys Val Tyr Asn
 2930 2935 2940
 Met Met Gly Lys Arg Glu Lys Lys Leu Gly Glu Phe Gly Lys Ala Lys
 2945 2950 2955 2960
 Gly Ser Arg Ala Ile Trp Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu
 2965 2970 2975

146

Phe	Glu	Ala	Leu	Gly	Phe	Leu	Asn	Glu	Asp	His	Trp	Phe	Ser	Arg	Glu
2980															
Asn	Ser	Leu	Ser	Gly	Val	Glu	Gly	Glu	Gly	Leu	His	Lys	Leu	Gly	Tyr
2985															
2990															
2995															
Ile	Leu	Arg	Asp	Val	Ser	Lys	Lys	Glu	Gly	Gly	Ala	Met	Tyr	Ala	Asp
3000															
3005															
3010															
Asp	Thr	Ala	Gly	Trp	Asp	Thr	Arg	Ile	Thr	Leu	Glu	Asp	Leu	Lys	Asn
3015															
3020															
3025															
Glu	Glu	Met	Val	Thr	Asn	His	Met	Glu	Gly	Glu	His	Lys	Lys	Leu	Ala
3030															
3035															
3040															
3045															
3050															
3055															
Glu	Ala	Ile	Phe	Lys	Leu	Thr	Tyr	Gln	Asn	Lys	Val	Val	Arg	Val	Gln
3060															
3065															
3070															
Arg	Pro	Thr	Pro	Arg	Gly	Thr	Val	Met	Asp	Ile	Ile	Ser	Arg	Arg	Asp
3075															
3080															
3085															
Gln	Arg	Gly	Ser	Gly	Gln	Val	Gly	Thr	Tyr	Gly	Leu	Asn	Thr	Phe	Thr
3090															
3095															
3100															
Asn	Met	Glu	Ala	Gln	Leu	Ile	Arg	Gln	Met	Glu	Gly	Glu	Gly	Val	Phe
3105															
3110															
3115															
Lys	Ser	Ile	Gln	His	Leu	Thr	Ile	Thr	Glu	Glu	Ile	Ala	Val	Gln	Asn
3120															
3125															
3130															
3135															
Trp	Leu	Ala	Arg	Val	Gly	Arg	Glu	Arg	Leu	Ser	Arg	Met	Ala	Ile	Ser
3140															
3145															
3150															
Gly	Asp	Asp	Cys	Val	Val	Lys	Pro	Leu	Asp	Asp	Arg	Phe	Ala	Ser	Ala
3155															
3160															
3165															
Leu	Thr	Ala	Leu	Asn	Asp	Met	Gly	Lys	Ile	Arg	Lys	Asp	Ile	Gln	Gln
3170															
3175															
3180															
Trp	Glu	Pro	Ser	Arg	Gly	Trp	Asn	Asp	Trp	Thr	Gln	Val	Pro	Phe	Cys
3185															
3190															
3195															
Ser	His	His	Phe	His	Glu	Leu	Ile	Met	Lys	Asp	Gly	Arg	Val	Leu	Val
3200															
3205															
3210															
3215															
Val	Pro	Cys	Arg	Asn	Gln	Asp	Glu	Leu	Ile	Gly	Arg	Ala	Arg	Ile	Ser
3220															
3225															
3230															
Gln	Gly	Ala	Gly	Trp	Ser	Leu	Arg	Glu	Thr	Ala	Cys	Leu	Gly	Lys	Ser
3235															
3240															
3245															
Tyr	Ala	Gln	Met	Trp	Ser	Leu	Met	Tyr	Phe	His	Arg	Arg	Asp	Leu	Arg
3250															
3255															
3260															
Leu	Ala	Ala	Asn	Ala	Ile	Cys	Ser	Ala	Val	Pro	Ser	His	Trp	Val	Pro
3265															
3270															
3275															
Thr	Ser	Arg	Thr	Thr	Trp	Ser	Ile	His	Ala	Lys	His	Glu	Trp	Met	Thr
3280															
3285															
3290															
Thr	Glu	Asp	Met	Leu	Thr	Val	Trp	Asn	Arg	Val	Trp	Ile	Gln	Glu	Asn
3300															
3305															
3310															
Pro	Trp	Met	Glu	Asp	Lys	Thr	Pro	Val	Glu	Ser	Trp	Glu	Glu	Ile	Pro
3315															
3320															
3325															
Tyr	Leu	Gly	Lys	Arg	Glu	Asp	Gln	Trp	Cys	Gly	Ser	Leu	Ile	Gly	Leu
3330															
3335															
3340															
Thr	Ser	Arg	Ala	Thr	Trp	Ala	Lys	Asn	Ile	Gln	Ala	Ala	Ile	Asn	Gln
3345															
3350															
3355															
Val	Arg	Ser	Leu	Ile	Gly	Asn	Glu	Glu	Tyr	Thr	Asp	Tyr	Met	Pro	Ser
3360															
3365															
3370															
3375															
Met	Lys	Arg	Phe	Arg	Arg	Glu	Glu	Glu	Glu	Ala	Gly	Val	Leu	Trp	
3380															
3385															

<210> 13

<211> 10723

147

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<221> CDS

<222> (97)...(10272)

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Met Asn Asn Gln Arg Lys	
1 5	
aag gcg aaa aac acg cct ttc aat atg ctg aaa cgc gag aga aac cgc	162
Lys Ala Lys Asn Thr Pro Phe Asn Met Leu Lys Arg Glu Arg Asn Arg	
10 15 20	
gtg tcg act gtg caa cag ctg aca aag aga ttc tca ctt gga atg ctg	210
Val Ser Thr Val Gln Gln Leu Thr Lys Arg Phe Ser Leu Gly Met Leu	
25 30 35	
cag gga cga gga cca tta aaa ctg ttc atg gcc ctg gtg gcg ttc ctt	258
Gln Gly Arg Gly Pro Leu Lys Leu Phe Met Ala Leu Val Ala Phe Leu	
40 45 50	
cgt ttc cta aca atc cca cca aca gca ggg ata ttg aag aga tgg gga	306
Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly Ile Leu Lys Arg Trp Gly	
55 60 65 70	
aca att aaa aaa tca aaa gct att aat gtt ttg aga ggg ttc agg aaa	354
Thr Ile Lys Lys Ser Lys Ala Ile Asn Val Leu Arg Gly Phe Arg Lys	
75 80 85	
gag att gga agg atg ctg aac atc ttg aat agg aga cgc aga tct gca	402
Glu Ile Gly Arg Met Leu Asn Ile Leu Asn Arg Arg Arg Arg Ser Ala	
90 95 100	
ggc atg atc att atg ctg att cca aca gtg atg gcg ttc cat tta acc	450
Gly Met Ile Ile Met Leu Ile Pro Thr Val Met Ala Phe His Leu Thr	
105 110 115	
aca cgt aac gga gaa cca cac atg atc gtc agc aga caa gag aaa ggg	498
Thr Arg Asn Gly Glu Pro His Met Ile Val Ser Arg Gln Glu Lys Gly	
120 125 130	
aaa agt ctt ctg ttt aaa aca gag gat ggc gtg aac atg tgt acc ctc	546
Lys Ser Leu Leu Phe Lys Thr Glu Asp Gly Val Asn Met Cys Thr Leu	
135 140 145 150	

148

atg gcc atg gac ctt ggt gaa ttg tgt gaa gac aca atc acg tac aag	594
Met Ala Met Asp Leu Gly Glu Leu Cys Glu Asp Thr Ile Thr Tyr Lys	
155 160 165	
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Cys Pro Leu Leu Arg Gln Asn Glu Pro Glu Asp Ile Asp Cys Trp Cys	
170 175 180	
aac tct acg tcc acg tgg gta act tat ggg acg tgt acc acc atg gga	690
Asn Ser Thr Ser Thr Trp Val Thr Tyr Gly Thr Cys Thr Thr Met Gly	
185 190 195	
gaa cat aga aga gaa aaa aga tca gtg gca ctc gtt cca cat gtg gga	738
Glu His Arg Arg Glu Lys Arg Ser Val Ala Leu Val Pro His Val Gly	
200 205 210	
atg gga ctg gag aca cga act gaa aca tgg atg tca tca gaa ggg gcc	786
Met Gly Leu Glu Thr Arg Thr Glu Thr Trp Met Ser Ser Glu Gly Ala	
215 220 225 230	
tgg aaa cat gtc cag aga att gaa act tgg atc ttg aga cat cca ggc	834
Trp Lys His Val Gln Arg Ile Glu Thr Trp Ile Leu Arg His Pro Gly	
235 240 245	
ttc acc atg atg gca gca atc ctg gca tac acc ata gga acg aca cat	882
Phe Thr Met Met Ala Ala Ile Leu Ala Tyr Thr Ile Gly Thr Thr His	
250 255 260	
ttc caa aga gcc ctg att ttc atc tta ctg aca gct gtc act cct tca	930
Phe Gln Arg Ala Leu Ile Phe Ile Leu Leu Thr Ala Val Thr Pro Ser	
265 270 275	
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Met Thr Met Arg Cys Ile Gly Met Ser Asn Arg Asp Phe Val Glu Gly	
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Val Ser Gly Gly Ser Trp Val Asp Ile Val Leu Glu His Gly Ser Cys	
295 300 305 310	
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Val Thr Thr Met Ala Lys Asn Lys Pro Thr Leu Asp Phe Glu Leu Ile	
315 320 325	
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Lys Thr Glu Ala Lys Gln Pro Ala Thr Leu Arg Lys Tyr Cys Ile Glu	
330 335 340	
gca aag cta acc aac aca aca aca gaa tct cgc tgc cca aca caa ggg	1170
Ala Lys Leu Thr Asn Thr Thr Thr Glu Ser Arg Cys Pro Thr Gln Gly	
345 350 355	
gaa ccc agc cta aat gaa gag cag gac aaa agg ttc gtc tgc aaa cac	1218
Glu Pro Ser Leu Asn Glu Gln Asp Lys Arg Phe Val Cys Lys His	
360 365 370	

149

tcc atg gta gac aga gga tgg gga aat gga tgt gga cta ttt gga aag Ser Met Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly Lys 375 380 385 390	1266
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gga aaa gtt gtg caa cca gaa aac ttg gaa tac acc att gtg ata aca Gly Lys Val Val Gln Pro Glu Asn Leu Glu Tyr Thr Ile Val Ile Thr 410 415 420	1362
cct cac tca ggg gaa gag cat gca gtc gga aat gac aca gga aaa cat Pro His Ser Gly Glu Glu His Ala Val Gly Asn Asp Thr Gly Lys His 425 430 435	1410
ggc aag gaa atc aaa ata aca cca cag agt tcc atc aca gaa gca gaa Gly Lys Glu Ile Lys Ile Thr Pro Gln Ser Ser Ile Thr Glu Ala Glu 440 445 450	1458
ttg aca ggt tat ggc act gtc aca atg gag tgc tct cca aga acg ggc Leu Thr Gly Tyr Gly Thr Val Thr Met Glu Cys Ser Pro Arg Thr Gly 455 460 465 470	1506
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ctg gtg cac agg caa tgg ttc cta gac ctg ccg tta cca tgg ttg ccc Leu Val His Arg Gln Trp Phe Leu Asp Leu Pro Leu Pro Trp Leu Pro 490 495 500	1602
gga gcg gac aca caa ggg tca aat tgg ata cag aaa gag aca ttg gtc Gly Ala Asp Thr Gln Gly Ser Asn Trp Ile Gln Lys Glu Thr Leu Val 505 510 515	1650
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tcc caa gaa ggg gcc atg cac aca gca ctt aca ggg gcc aca gaa atc Ser Gln Glu Gly Ala Met His Thr Ala Leu Thr Gly Ala Thr Glu Ile 535 540 545 550	1746
caa atg tca tca gga aac tta ctc ttc aca gga cat ctc aag tgc agg Gln Met Ser Ser Gly Asn Leu Leu Phe Thr Gly His Leu Lys Cys Arg 555 560 565	1794
ctg aga atg gac aag cta cag ctc aaa gga atg tca tac tct atg tgc Leu Arg Met Asp Lys Leu Gln Leu Lys Gly Met Ser Tyr Ser Met Cys 570 575 580	1842

150

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Thr Gly Lys Phe Lys Val Val Lys Glu Ile Ala Glu Thr Gln His Gly	
585 590 595	
aca ata gtt atc aga gtg caa tat gaa ggg gac ggc tct cca tgc aag	1938
Thr Ile Val Ile Arg Val Gln Tyr Glu Gly Asp Gly Ser Pro Cys Lys	
600 605 610	
atc cct ttt gag ata atg gat ttg gaa aaa aga cat gtc tta ggt cgc	1986
Ile Pro Phe Glu Ile Met Asp Leu Glu Lys Arg His Val Leu Gly Arg	
615 620 625 630	
ctg att aca gtc aac cca att gtg aca gaa aaa gat agc cca gtc aac	2034
Leu Ile Thr Val Asn Pro Ile Val Thr Glu Lys Asp Ser Pro Val Asn	
635 640 645	
ata gaa gca gaa cct cca ttc gga gac agc tac atc atc ata gga gta	2082
Ile Glu Ala Glu Pro Pro Phe Gly Asp Ser Tyr Ile Ile Ile Gly Val	
650 655 660	
gag cgg gga caa ctg aag ctc aac tgg ttt aag aaa gga agt tct atc	2130
Glu Pro Gly Gln Leu Lys Leu Asn Trp Phe Lys Lys Gly Ser Ser Ile	
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680 685 690	
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Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser Leu Gly Gly Val Phe Thr	
695 700 705 710	
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Ser Ile Gly Lys Ala Leu His Gln Val Phe Gly Ala Ile Tyr Gly Ala	
715 720 725	
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Ala Phe Ser Gly Val Ser Trp Thr Met Lys Ile Leu Ile Gly Val Ile	
730 735 740	
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Ile Thr Trp Ile Gly Met Asn Ser Arg Ser Thr Ser Leu Ser Val Thr	
745 750 755	
cta gta ttg gtg gga att gtg aca ctg tat ttg gga gtc atg gtg cag	2418
Leu Val Leu Val Gly Ile Val Thr Leu Tyr Leu Gly Val Met Val Gln	
760 765 770	
gcc gat agt ggt tgc gtt gtg agc tgg aaa aac aaa gaa ctg aaa tgt	2466
Ala Asp Ser Gly Cys Val Val Ser Trp Lys Asn Lys Glu Leu Lys Cys	
775 780 785 790	
ggc agt ggg att ttc atc aca gac aac gtg cac aca tgg aca gaa caa	2514
Gly Ser Gly Ile Phe Ile Thr Asp Asn Val His Thr Trp Thr Glu Gln	
795 800 805	

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aaa gcc cat gaa gag ggc att tgt gga atc cgc tca gta aca aga ctg Lys Ala His Glu Glu Gly Ile Cys Gly Ile Arg Ser Val Thr Arg Leu 825 830 835	2610
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atc atg cag gca gga aaa cga tct ctg cgg cct cag ccc act gag ctg Ile Met Gln Ala Gly Lys Arg Ser Leu Arg Pro Gln Pro Thr Glu Leu 875 880 885	2754
aag tat tca tgg aaa aca tgg ggc aaa gca aaa atg ctc tct aca gag Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala Lys Met Leu Ser Thr Glu 890 895 900	2802
tct cat aac cag acc ttt ctc att gat ggc ccc gaa aca gca gaa tgc Ser His Asn Gln Thr Phe Leu Ile Asp Gly Pro Glu Thr Ala Glu Cys 905 910 915	2850
ccc aac aca aat aga gct tgg aat tcg ttg gaa gtt gaa gac tat ggc Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu Glu Val Glu Asp Tyr Gly 920 925 930	2898
ttt gga gta ttc acc acc aat ata tgg cta aaa ttg aaa gaa aaa cag Phe Gly Val Phe Thr Thr Asn Ile Trp Leu Lys Leu Lys Glu Lys Gln 935 940 945 950	2946
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aga gcc gtc cat gcc gat atg ggt tat tgg ata gaa agt gca ctc aat Arg Ala Val His Ala Asp Met Gly Tyr Trp Ile Glu Ser Ala Leu Asn 970 975 980	3042
gac aca tgg aag ata gag aaa gcc tct ttc att gaa gtt aaa aac tgc Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe Ile Glu Val Lys Asn Cys 985 990 995	3090
cac tgg cca aaa tca cac acc ctc tgg agc aat gga gtg cta gaa agt His Trp Pro Lys Ser His Thr Leu Trp Ser Asn Gly Val Leu Glu Ser 1000 1005 1010	3138

152

gag atg ata att cca aag aat ctc gct gga cca gtg tct caa cac aac Glu Met Ile Ile Pro Lys Asn Leu Ala Gly Pro Val Ser Gln His Asn 1015 1020 1025 1030 1036
tat aga cca ggc tac cat aca caa ata aca gga cca tgg cat cta ggt Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr Gly Pro Trp His Leu Gly 1035 1040 1045 3234
aag ctt gag atg gac ttt gat ttc tgt gat gga aca aca gtg gta gtg Lys Leu Glu Met Asp Phe Asp Phe Cys Asp Gly Thr Thr Val Val Val 1050 1055 1060 3282
act gag gac tgc gga aat aga gga ccc tct ttg aga aca acc act gcc Thr Glu Asp Cys Gly Asn Arg Gly Pro Ser Leu Arg Thr Thr Thr Ala 1065 1070 1075 3330
tct gga aaa ctc ata aca gaa tgg tgc tgc cga tct tgc aca tta cca Ser Gly Lys Leu Ile Thr Glu Trp Cys Cys Arg Ser Cys Thr Leu Pro 1080 1085 1090 3378
ccg cta aga tac aga ggt gag gat ggg tgc tgg tac ggg atg gaa atc Pro Leu Arg Tyr Arg Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile 1095 1100 1105 1110 3426
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tcc cag agc acc ata cca gag acc att ctt gag ttg act gat gcg tta Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu Glu Leu Thr Asp Ala Leu 1240 1245 1250	3858
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154

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gat gga gcc tat aga att aag caa aaa ggg att ctt gga tat tcc cag Asp Gly Ala Tyr Arg Ile Lys Gln Lys Gly Ile Leu Gly Tyr Ser Gln 1495 1500 1505 1510	4626
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155

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156

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gaa atc tgg aca aaa gaa ggg gaa agg aag aaa ttg aaa ccc aga tgg Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp 2055 2060 2065 2070	6306
ttg gat gct agg atc tat tct gac cca ctg cgc cta aaa gaa ttt aag Leu Asp Ala Arg Ile Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys 2075 2080 2085	6354
gaa ttt gca gcc gga aga aag tct ctg acc ctg aac cta atc aca gaa Glu Phe Ala Ala Gly Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu 2090 2095 2100	6402

atg ggt agg ctc cca acc ttc atg act cag aag gca aga gac gca ctg Met Gly Arg Leu Pro Thr Phe Met Thr Gln Lys Ala Arg Asp Ala Leu 2105 2110 2115	6450
gac aac tta gca gtg ctg cac acg gct gag gca ggt gga agg gog tac Asp Asn Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala Tyr 2120 2125 2130	6498
aac cat gct ctc agt gaa ctg cgg gag acc ctg gag aca ttg ctt tta Asn His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu Leu Leu 2135 2140 2145 2150	6546
ctg aca ctt ctg gct aca gtc acg gga ggg atc ttt tta ttc ttg atg Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu Phe Leu Met 2155 2160 2165	6594
agc gga agg ggc ata ggg aag atg acc ctg gga atg tgc tgc ata atc Ser Gly Arg Gly Ile Gly Lys Met Thr Leu Gly Met Cys Cys Ile Ile 2170 2175 2180	6642
acg gct agc atc ctc cta tgg tac gca caa ata cag cca cac tgg ata Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln Ile Gln Pro His Trp Ile 2185 2190 2195	6690
gca gct tca ata ata ctg gag ttt ttt ctc ata gtt ttg ctt att cca Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Ile Val Leu Leu Ile Pro 2200 2205 2210	6738
gaa cct gaa aaa cag aga aca ccc caa gac aac caa ctg acc tac gtt Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn Gln Leu Thr Tyr Val 2215 2220 2225 2230	6786
gtc ata gcc atc ctc aca gtg gtg gcc gca acc atg gca aac gag atg Val Ile Ala Ile Leu Thr Val Val Ala Ala Thr Met Ala Asn Glu Met 2235 2240 2245	6834
ggt ttc cta gaa aaa acg aag aaa gat ctc gga ttg gga agc att gca Gly Phe Leu Glu Lys Thr Lys Lys Asp Leu Gly Leu Gly Ser Ile Ala 2250 2255 2260	6882
acc cag caa ccc gag agc aac atc ctg gac ata gat cta cgt cct gca Thr Gln Gln Pro Glu Ser Asn Ile Leu Asp Ile Asp Leu Arg Pro Ala 2265 2270 2275	6930
tca gca tgg acg ctg tat gcc gtg gcc aca aca ttt gtt aca cca atg Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Phe Val Thr Pro Met 2280 2285 2290	6978
ttg aga cat agc att gaa aat tcc tca gtg aat gtg tcc cta aca gct Leu Arg His Ser Ile Glu Asn Ser Ser Val Asn Val Ser Leu Thr Ala 2295 2300 2305 2310	7026

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ata gcc aac caa gcc aca gtg tta atg ggt ctc ggg aaa gga tgg cca Ile Ala Asn Gln Ala Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro 2315 2320 2325	7074
ttg tca aag atg gac atc gga gtt ccc ctt ctc gcc att gga tgc tac Leu Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala Ile Gly Cys Tyr 2330 2335 2340	7122
tca caa gtc aac ccc ata act ctc aca gca gct ctt ttc tta ttg gta Ser Gln Val Asn Pro Ile Thr Leu Thr Ala Ala Leu Phe Leu Leu Val 2345 2350 2355	7170
gca cat tat gcc atc ata ggg cca gga ctc caa gca aaa gca acc aga Ala His Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg 2360 2365 2370	7218
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gat gga ata aca gtg att gac cta gat cca ata cct tat gat cca aag Asp Gly Ile Thr Val Ile Asp Leu Asp Pro Ile Pro Tyr Asp Pro Lys 2395 2400 2405	7314
ttt gaa aag cag ttg gga caa gta atg ctc cta gtc ctc tgc gtg act Phe Glu Lys Gln Leu Gly Gln Val Met Leu Leu Val Leu Cys Val Thr 2410 2415 2420	7362
caa gta ttg atg atg agg act aca tgg gct ctg tgt gag gct tta acc Gln Val Leu Met Met Arg Thr Thr Trp Ala Leu Cys Glu Ala Leu Thr 2425 2430 2435	7410
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acc aac aca aga agg gga act ggc aac ata gga gag acg ctt gga gag Thr Asn Thr Arg Arg Gly Thr Gly Asn Ile Gly Glu Thr Leu Gly Glu 2490 2495 2500	7602
aaa tgg aaa agc cga ttg aac gca ttg gga aaa agt gaa ttc cag atc Lys Trp Lys Ser Arg Leu Asn Ala Leu Gly Lys Ser Glu Phe Gln Ile 2505 2510 2515	7650
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ggc att aaa aga gga gaa acg gac cat cac gct gtg tgg cga ggc tca Gly Ile Lys Arg Gly Glu Thr Asp His His Ala Val Ser Arg Gly Ser 2535 2540 2545 2550	7746
gca aaa ctg aga tgg ttc gtt gag aga aac atg gtc aca cca gaa ggg Ala Lys Leu Arg Trp Phe Val Glu Arg Asn Met Val Thr Pro Glu Gly 2555 2560 2565	7794
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cca gga cac gaa gaa ccc atc ccc atg tca aca tat ggg tgg aat cta Pro Gly His Glu Glu Pro Ile Pro Met Ser Thr Tyr Gly Trp Asn Leu 2600 2605 2610	7938
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tgt gac aca tta ttg tgt gac ata ggg gag tca tca cca aat ccc aca Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro Thr 2635 2640 2645	8034
gtg gaa gca gga cga aca ctc aga gtc ctt aac tta gta gaa aat tgg Val Glu Ala Gly Arg Thr Leu Arg Val Leu Asn Leu Val Glu Asn Trp 2650 2655 2660	8082
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ccc tca gtc ata gaa aaa atg gaa gca cta caa agg aaa tat gga gga Pro Ser Val Ile Glu Lys Met Glu Ala Leu Gln Arg Lys Tyr Gly Gly 2680 2685 2690	8178
gcc tta gtg agg aat cca ctc tca cga aac tcc aca cat gag atg tac Ala Leu Val Arg Asn Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr 2695 2700 2705 2710	8226
tgg gta tcc aat gct tcc ggg aac ata gtg tca tca gtg aac atg att Trp Val Ser Asn Ala Ser Gly Asn Ile Val Ser Ser Val Asn Met Ile 2715 2720 2725	8274
tca agg atg ttg atc aac aga ttt aca atg aga tac aag aaa gcc act Ser Arg Met Leu Ile Asn Arg Phe Thr Met Arg Tyr Lys Lys Ala Thr 2730 2735 2740	8322

160

tac gag ccg gat gtt gac ctc gga agc gga acc cgt aac atc ggg att	8370
Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly Thr Arg Asn Ile Gly Ile	
2745 2750 2755	
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Glu Ser Glu Ile Pro Asn Leu Asp Ile Ile Gly Lys Arg Ile Glu Lys	
2760 2765 2770	
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Ile Lys Gln Glu His Glu Thr Ser Trp His Tyr Asp Gln Asp His Pro	
2775 2780 2785 2790	
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Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly	
2795 2800 2805	
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Ser Ala Ser Ser Met Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro	
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Trp Asp Val Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr	
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Pro Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr	
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Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu Met Lys Ile Thr Ala Glu	
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tgg ctt tgg aaa gaa tta ggg aag aaa aag aca ccc agg atg tgc acc	8754
Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys Thr Pro Arg Met Cys Thr	
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Arg Glu Glu Phe Thr Arg Lys Val Arg Ser Asn Ala Ala Leu Gly Ala	
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Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser Ala Arg Glu Ala Val Glu	
2905 2910 2915	
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2920 2925 2930	
gaa gga aag tgt gaa aca tgt gtg tac aac atg atg gga aaa aga gag	8946
Glu Gly Lys Cys Glu Thr Cys Val Tyr Asn Met Met Gly Lys Arg Glu	
2935 2940 2945 2950	
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Lys Lys Leu Gly Glu Phe Gly Lys Ala Lys Gly Ser Arg Ala Ile Trp	
2955 2960 2965	

161

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tti aat gaa gat cac tgg ttc tcc aga gag aac tcc ctg agt gga gtg Leu Asn Glu Asp His Trp Phe Ser Arg Glu Asn Ser Leu Ser Gly Val 2985 2990 2995	9090
gaa gga gaa ggg ctg cac aag cta ggt tac att cta aga gac gtg agc Glu Gly Glu Gly Leu His Lys Leu Gly Tyr Ile Leu Arg Asp Val Ser 3000 3005 3010	9138
aag aaa gag gga gga gca atg tat gcc gat gac acc gca gga tgg gat Lys Lys Glu Gly Gly Ala Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp 3015 3020 3025 3030	9186
aca aga atc aca cta gaa gac cta aaa aat gaa gaa atg gta aca aac Thr Arg Ile Thr Leu Glu Asp Leu Lys Asn Glu Met Val Thr Asn 3035 3040 3045	9234
cac atg gaa gga gaa cac aag aaa cta gcc gag gcc att ttc aaa cta His Met Glu Gly Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu 3050 3055 3060	9282
acg tac caa aac aag gtg gtg cgt gtg caa aga cca aca cca aga ggc Thr Tyr Gln Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly 3065 3070 3075	9330
aca gta atg gac atc ata tcg aga aga gac caa aga ggt agt gga caa Thr Val Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly Gln 3080 3085 3090	9378
gtt ggc acc tat gga ctc aat act ttc acc aat atg gaa gcc caa cta Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu 3095 3100 3105 3110	9426
atc aga cag atg gag gga gaa gga gtc ttt aaa agc att cag cac cta Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile Gln His Leu 3115 3120 3125	9474
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162

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gat gaa ctg att ggc aga gcc cga atc tcc caa gga gca ggg tgg tct Asp Glu Leu Ile Gly Arg Ala Arg Ile Ser Gln Gly Ala Gly Trp Ser 3225 3230 3235	9810
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gac caa tgg tgc ggc tca ttg att ggg tta aca agc agg gcc acc tgg Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala Thr Trp 3335 3340 3345 3350	10146
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aat gaa gaa tac aca gat tac atg cca tcc atg aaa aga ttc aga aga Asn Glu Glu Tyr Thr Asp Tyr Met Pro Ser Met Lys Arg Phe Arg Arg 3370 3375 3380	10242
gaa gag gaa gaa gca gga gtt ctg tgg tag aaagcaaaac taacatgaaa Glu Glu Glu Glu Ala Gly Val Leu Trp * 3385 3390	10292

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gaggagaccc ccccgaaaca aaaaacagca tattgacgct ggggaagacc agagatccctg 10652
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caacaggttc t 10723

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<210> 14
 <211> 3391
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:/Note =
 synthetic construct

<400> 14

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			20					25					30		
Phe	Ser	Leu	Gly	Met	Leu	Gln	Gly	Arg	Gly	Pro	Leu	Lys	Leu	Phe	Met
		35					40					45			
Ala	Leu	Val	Ala	Phe	Leu	Arg	Phe	Leu	Thr	Ile	Pro	Pro	Thr	Ala	Gly
		50				55				60					
Ile	Leu	Lys	Arg	Trp	Gly	Thr	Ile	Lys	Lys	Ser	Lys	Ala	Ile	Asn	Val
65					70					75				80	
Leu	Arg	Gly	Phe	Arg	Lys	Glu	Ile	Gly	Arg	Met	Leu	Asn	Ile	Leu	Asn
			85					90					95		
Arg	Arg	Arg	Arg	Ser	Ala	Gly	Met	Ile	Ile	Met	Leu	Ile	Pro	Thr	Val
			100					105					110		
Met	Ala	Phe	His	Leu	Thr	Thr	Arg	Asn	Gly	Glu	Pro	His	Met	Ile	Val
		115					120					125			
Ser	Arg	Gln	Glu	Lys	Gly	Lys	Ser	Leu	Leu	Phe	Lys	Thr	Glu	Asp	Gly
		130				135					140				
Val	Asn	Met	Cys	Thr	Leu	Met	Ala	Met	Asp	Leu	Gly	Glu	Leu	Cys	Glu
145					150					155				160	
Asp	Thr	Ile	Thr	Tyr	Lys	Cys	Pro	Leu	Leu	Arg	Gln	Asn	Glu	Pro	Glu
				165					170					175	
Asp	Ile	Asp	Cys	Trp	Cys	Asn	Ser	Thr	Ser	Thr	Trp	Val	Thr	Tyr	Gly
		180						185					190		
Thr	Cys	Thr	Thr	Met	Gly	Glu	His	Arg	Arg	Glu	Lys	Arg	Ser	Val	Ala
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Leu	Val	Pro	His	Val	Gly	Met	Gly	Leu	Glu	Thr	Arg	Thr	Glu	Thr	Trp
		210				215					220				
Met	Ser	Ser	Glu	Gly	Ala	Trp	Lys	His	Val	Gln	Arg	Ile	Glu	Thr	Trp
225					230					235				240	
Ile	Leu	Arg	His	Pro	Gly	Phe	Thr	Met	Met	Ala	Ala	Ile	Leu	Ala	Tyr
					245					250				255	
Thr	Ile	Gly	Thr	Thr	His	Phe	Gln	Arg	Ala	Leu	Ile	Phe	Ile	Leu	Leu
			260					265					270		

164

Thr Ala Val Thr Pro Ser Met Thr Met Arg Cys Ile Gly Met Ser Asn
 275 280 285
 Arg Asp Phe Val Glu Gly Val Ser Gly Gly Ser Trp Val Asp Ile Val
 290 295 300
 Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr
 305 310 315 320
 Leu Asp Phe Glu Leu Ile Lys Thr Glu Ala Lys Gln Pro Ala Thr Leu
 325 330 335
 Arg Lys Tyr Cys Ile Glu Ala Lys Leu Thr Asn Thr Thr Thr Glu Ser
 340 345 350
 Arg Cys Pro Thr Gln Gly Glu Pro Ser Leu Asn Glu Glu Gln Asp Lys
 355 360 365
 Arg Phe Val Cys Lys His Ser Met Val Asp Arg Gly Trp Gly Asn Gly
 370 375 380
 Cys Gly Leu Phe Gly Lys Gly Gly Ile Val Thr Cys Ala Met Phe Arg
 385 390 395 400
 Cys Lys Lys Asn Met Glu Gly Lys Val Val Gln Pro Glu Asn Leu Glu
 405 410 415
 Tyr Thr Ile Val Ile Thr Pro His Ser Gly Glu Glu His Ala Val Gly
 420 425 430
 Asn Asp Thr Gly Lys His Gly Lys Glu Ile Lys Ile Thr Pro Gln Ser
 435 440 445
 Ser Ile Thr Glu Ala Glu Leu Thr Gly Tyr Gly Thr Val Thr Met Glu
 450 455 460
 Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Gln
 465 470 475 480
 Met Glu Asn Lys Ala Trp Leu Val His Arg Gln Trp Phe Leu Asp Leu
 485 490 495
 Pro Leu Pro Trp Leu Pro Gly Ala Asp Thr Gln Gly Ser Asn Trp Ile
 500 505 510
 Gln Lys Glu Thr Leu Val Thr Phe Lys Asn Pro His Ala Lys Lys Gln
 515 520 525
 Asp Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu
 530 535 540
 Thr Gly Ala Thr Glu Ile Gln Met Ser Ser Gly Asn Leu Leu Phe Thr
 545 550 555 560
 Gly His Leu Lys Cys Arg Leu Arg Met Asp Lys Leu Gln Leu Lys Gly
 565 570 575
 Met Ser Tyr Ser Met Cys Thr Gly Lys Phe Lys Val Val Lys Glu Ile
 580 585 590
 Ala Glu Thr Gln His Gly Thr Ile Val Ile Arg Val Gln Tyr Glu Gly
 595 600 605
 Asp Gly Ser Pro Cys Lys Ile Pro Phe Glu Ile Met Asp Leu Glu Lys
 610 615 620
 Arg His Val Leu Gly Arg Leu Ile Thr Val Asn Pro Ile Val Thr Glu
 625 630 635 640
 Lys Asp Ser Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Asp Ser
 645 650 655
 Tyr Ile Ile Ile Gly Val Glu Pro Gly Gln Leu Lys Leu Asn Trp Phe
 660 665 670
 Lys Lys Gly Ser Ser Ile Gly Gln Met Phe Glu Thr Thr Met Arg Gly
 675 680 685
 Ala Lys Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser
 690 695 700

165

Leu Gly Gly Val Phe Thr Ser Ile Gly Lys Ala Leu His Gln Val Phe
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 Gly Ala Ile Tyr Gly Ala Ala Phe Ser Gly Val Ser Trp Thr Met Lys
 725 730 735
 Ile Leu Ile Gly Val Ile Ile Thr Trp Ile Gly Met Asn Ser Arg Ser
 740 745 750
 Thr Ser Leu Ser Val Thr Leu Val Leu Val Gly Ile Val Thr Leu Tyr
 755 760 765
 Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys
 770 775 780
 Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val
 785 790 795 800
 His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys
 805 810 815
 Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Gly Ile Cys Gly Ile
 820 825 830
 Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro
 835 840 845
 Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met
 850 855 860
 Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg
 865 870 875 880
 Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala
 885 890 895
 Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly
 900 905 910
 Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu
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 Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser
 945 950 955 960
 Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp
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 980 985 990
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 995 1000 1005
 Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala Gly
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 Pro Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr
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 Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr Arg Gly Glu Asp Gly Cys
 1090 1095 1100
 Trp Tyr Gly Met Glu Ile Arg Pro Leu Lys Glu Lys Glu Glu Asn Leu
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 Val Asn Ser Leu Val Thr Ala Gly His Gly Gln Val Asp Asn Phe Ser
 1125 1130 1135

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 1170 1175 1180
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 Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu Trp Lys Glu Gly Glu
 1555 1560 1565

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 Lys Ala Gly Asn Asp Ile Ala Ala Cys Leu Arg Lys Asn Gly Lys Lys
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 Pro Met Pro Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile
 1925 1930 1935
 Gly Arg Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu
 1940 1945 1950
 Pro Leu Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met
 1955 1960 1965
 Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met Phe
 1970 1975 1980
 Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu
 1985 1990 1995 2000

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 Leu Ala Ala Asn Ala Ile Cys Ser Ala Val Pro Ser His Trp Val Pro
 3265 3270 3275 3280
 Thr Ser Arg Thr Thr Trp Ser Ile His Ala Lys His Glu Trp Met Thr
 3285 3290 3295

171

Thr Glu Asp Met Leu Thr Val Trp Asn Arg Val Trp Ile Gln Glu Asn
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 Tyr Leu Gly Lys Arg Glu Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu
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<223> Description of Artificial Sequence:/Note =
 synthetic construct

<221> CDS

<222> (97)...(10272)

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 gttcotaacag ttttttaatt agagagcaga tctctg atg aat aac caa cgg aaa 114
 Met Asn Asn Gln Arg Lys
 1 5

aag gcg aaa aac acg cct ttc aat atg ctg aaa cgc gag aga aac cgc 162
 Lys Ala Lys Asn Thr Pro Phe Asn Met Leu Lys Arg Glu Arg Asn Arg
 10 15 20

gtg tcg act gtg caa cag ctg aca aag aga ttc tca ctt gga atg ctg 210
 Val Ser Thr Val Gln Gln Leu Thr Lys Arg Phe Ser Leu Gly Met Leu
 25 30 35

cag gga cga gga cca tta aaa ctg ttc atg gcc ctg gtg gcg ttc ctt 258
 Gln Gly Arg Gly Pro Leu Lys Leu Phe Met Ala Leu Val Ala Phe Leu
 40 45 50

cgt ttc cta aca atc cca cca aca gca ggg ata ttg aag aga tgg gga 306
 Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly Ile Leu Lys Arg Trp Gly
 55 60 65 70

aca att aaa aaa tca aaa gct att aat gtt ttg aga ggg ttc agg aaa 354
 Thr Ile Lys Lys Ser Lys Ala Ile Asn Val Leu Arg Gly Phe Arg Lys
 75 80 85

gag att gga agg atg ctg aac atc ttg aat agg aga cgc aga tct gca 402
 Glu Ile Gly Arg Met Leu Asn Ile Leu Asn Arg Arg Arg Arg Ser Ala
 90 95 100

172

ggc atg atc att atg ctg att cca aca gtg atg gcg ttc cat tta acc	450
Gly Met Ile Ile Met Leu Ile Pro Thr Val Met Ala Phe His Leu Thr	
105 110 115	
aca cgt aac gga gaa cca cac atg atc gtc agc aga caa gag aaa ggg	498
Thr Arg Asn Gly Glu Pro His Met Ile Val Ser Arg Gln Glu Lys Gly	
120 125 130	
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Lys Ser Leu Leu Phe Lys Thr Glu Val Gly Val Asn Met Cys Thr Leu	
135 140 145 150	
atg gcc atg gac ctt ggt gaa ttg tgt gaa gac aca atc acg tac aag	594
Met Ala Met Asp Leu Gly Glu Leu Cys Glu Asp Thr Ile Thr Tyr Lys	
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Cys Pro Leu Leu Arg Gln Asn Glu Pro Glu Asp Ile Asp Cys Trp Cys	
170 175 180	
aac tct acg tcc acg tgg gta act tat ggg acg tgt acc acc atg gga	690
Asn Ser Thr Ser Thr Trp Val Thr Tyr Gly Thr Cys Thr Thr Met Gly	
185 190 195	
gaa cat aga aga gaa aaa aga tca gtg gca ctc gtt cca cat gtg gga	738
Glu His Arg Arg Glu Lys Arg Ser Val Ala Leu Val Pro His Val Gly	
200 205 210	
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Met Gly Leu Glu Thr Arg Thr Glu Thr Trp Met Ser Ser Glu Gly Ala	
215 220 225 230	
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Met Thr Met Arg Cys Ile Gly Met Ser Asn Arg Asp Phe Val Glu Gly	
280 285 290	
gtt tca gga gga agc tgg gtt gac ata gtc tta gaa cat gga agc tgt	1026
Val Ser Gly Gly Ser Trp Val Asp Ile Val Leu Glu His Gly Ser Cys	
295 300 305 310	

173

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Val Thr Thr Met Ala Lys Asn Lys Pro Thr Leu Asp Phe Glu Leu Ile	
315 320 325	
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Lys Thr Glu Ala Lys Gln Pro Ala Thr Leu Arg Lys Tyr Cys Ile Glu	
330 335 340	
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375 380 385 390	
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Gly Gly Ile Val Thr Cys Ala Met Phe Arg Cys Lys Lys Asn Met Glu	
395 400 405	
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Gly Lys Val Val Gln Pro Glu Asn Leu Glu Tyr Thr Ile Val Ile Thr	
410 415 420	
cct cac tca ggg gaa gag cat gca gtc gga aat gac aca gga aaa cat	1410
Pro His Ser Gly Glu Glu His Ala Val Gly Asn Asp Thr Gly Lys His	
425 430 435	
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Gly Lys Glu Ile Lys Ile Thr Pro Gln Ser Ser Ile Thr Glu Ala Glu	
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Leu Thr Gly Tyr Gly Thr Val Thr Met Glu Cys Ser Pro Arg Thr Gly	
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Leu Asp Phe Asn Glu Met Val Leu Leu Gln Met Glu Asn Lys Ala Trp	
475 480 485	
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505 510 515	
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175

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tct cat aac cag acc ttt ctc att gat ggc ccc gaa aca gca gaa tgc ser his asn gln thr phe leu ile asp gly pro glu thr ala glu cys 905 910 915	2850
ccc aac aca aat aga gct tgg aat tcg ttg gaa gtt gaa gac tat ggc pro asn thr asn arg ala trp asn ser leu glu val glu asp tyr gly 920 925 930	2898
ttt gga gta ttc acc acc aat ata tgg cta aaa ttg aaa gaa aaa cag phe gly val phe thr thr asn ile trp leu lys leu lys glu lys gln 935 940 945 950	2946
gat gta ttc tgc gac tca aaa ctc atg tca cgc gcc ata aaa gac aac asp val phe cys asp ser lys leu met ser ala ala ile lys asp asn 955 960 965	2994

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aga gcc gtc cat gcc gat atg ggt tat tgg ata gaa agt gca ctc aat Arg Ala Val His Ala Asp Met Gly Tyr Trp Ile Glu Ser Ala Leu Asn 970 975 980	3042
gac aca tgg aag ata gag aaa gcc tct ttc att gaa gtt aaa aac tgc Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe Ile Glu Val Lys Asn Cys 985 990 995	3090
cac tgg cca aaa tca cac acc ctc tgg agc aat gga gtg cta gaa agt His Trp Pro Lys Ser His Thr Leu Trp Ser Asn Gly Val Leu Glu Ser 1000 1005 1010	3138
gag atg ata att cca aag aat ctc gct gga cca gtg tct caa cac aac Glu Met Ile Ile Pro Lys Asn Leu Ala Gly Pro Val Ser Gln His Asn 1015 1020 1025 1030	3186
tat aga cca ggc tac cat aca caa ata aca gga cca tgg cat cta ggt Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr Gly Pro Trp His Leu Gly 1035 1040 1045	3234
aag ctt gag atg gac ttt gat ttc tgt gat gga aca aca gtg gta gtg Lys Leu Glu Met Asp Phe Asp Phe Cys Asp Gly Thr Thr Val Val Val 1050 1055 1060	3282
act gag gac tgc gga aat aga gga ccc tct ttg aga aca acc act gcc Thr Glu Asp Cys Gly Asn Arg Gly Pro Ser Leu Arg Thr Thr Thr Ala 1065 1070 1075	3330
tct gga aaa ctc ata aca gaa tgg tgc tgc cga tct tgc aca tta cca Ser Gly Lys Leu Ile Thr Glu Trp Cys Cys Arg Ser Cys Thr Leu Pro 1080 1085 1090	3378
cag cta aga tac aga ggt gag gat ggg tgc tgg tac ggg atg gaa atc Pro Leu Arg Tyr Arg Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile 1095 1100 1105 1110	3426
aga cca ttg aag gag aaa gaa gag aat ttg gtc aac tcc ttg gtc aca Arg Pro Leu Lys Glu Lys Glu Glu Asn Leu Val Asn Ser Leu Val Thr 1115 1120 1125	3474
gct gga cat ggg cag gtc gac aac ttt tca cta gga gtc ttg gga atg Ala Gly His Gly Gln Val Asp Asn Phe Ser Leu Gly Val Leu Gly Met 1130 1135 1140	3522
gca ttg ttc ctg gag gaa atg ctt agg acc cga gta gga acg aaa cat Ala Leu Phe Leu Glu Glu Met Leu Arg Thr Arg Val Gly Thr Lys His 1145 1150 1155	3570
gca ata cta cta gtt gca gtt tct ttt gtg aca ttg atc aca ggg aac Ala Ile Leu Leu Val Ala Val Ser Phe Val Thr Leu Ile Thr Gly Asn 1160 1165 1170	3618

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atg tcc ttt aga gac ctg gga aga gtg atg gtt atg gta ggc gcc act Met Ser Phe Arg Asp Leu Gly Arg Val Met Val Met Val Gly Ala Thr 1175 1180 1185 1190	3666
atg acg gat gac ata ggt atg ggc gtg act tat ctt gcc cta cta gca Met Thr Asp Asp Ile Gly Met Gly Val Thr Tyr Leu Ala Leu Leu Ala 1195 1200 1205	3714
gcc ttc aaa gtc aga cca act ttt gca gct gga cta ctc ttg aga aag Ala Phe Lys Val Arg Pro Thr Phe Ala Ala Gly Leu Leu Leu Arg Lys 1210 1215 1220	3762
ctg acc tcc aag gaa ttg atg atg act act ata gga att gta ctc ctc Leu Thr Ser Lys Glu Leu Met Met Thr Thr Ile Gly Ile Val Leu Leu 1225 1230 1235	3810
tcc cag agc acc ata cca gag acc att ctt gag ttg act gat gcg tta Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu Glu Leu Thr Asp Ala Leu 1240 1245 1250	3858
gcc tta ggc atg atg gtc ctc aaa atg gtg aga aat atg gaa aag tat Ala Leu Gly Met Met Val Leu Lys Met Val Arg Asn Met Glu Lys Tyr 1255 1260 1265 1270	3906
caa ttg gca gtg act atc atg gct atc ttg tgc gtc cca aac gca gtg Gln Leu Ala Val Thr Ile Met Ala Ile Leu Cys Val Pro Asn Ala Val 1275 1280 1285	3954
ata tta caa aac gca tgg aaa gtg agt tgc aca ata ttg gca gtg gtg Ile Leu Gln Asn Ala Trp Lys Val Ser Cys Thr Ile Leu Ala Val Val 1290 1295 1300	4002
tcc gtt tcc cca ctg ttc tta aca tcc tca cag caa aaa aca gat tgg Ser Val Ser Pro Leu Phe Leu Thr Ser Ser Gln Gln Lys Thr Asp Trp 1305 1310 1315	4050
ata cca tta gca ttg acg atc aaa ggt ctc aat cca aca gct att ttt Ile Pro Leu Ala Leu Thr Ile Lys Gly Leu Asn Pro Thr Ala Ile Phe 1320 1325 1330	4098
cta aca acc ctc tca aga acc agc aag aaa agg agc tgg cca tta aat Leu Thr Thr Leu Ser Arg Thr Ser Lys Lys Arg Ser Trp Pro Leu Asn 1335 1340 1345 1350	4146
gag gct atc atg gca gtc ggg atg gtg agc att tta gcc agt tct ctc Glu Ala Ile Met Ala Val Gly Met Val Ser Ile Leu Ala Ser Ser Leu 1355 1360 1365	4194
cta aaa aat gat att ccc atg aca gga cca tta gtg gct gga ggg ctc Leu Lys Asn Asp Ile Pro Met Thr Gly Pro Leu Val Ala Gly Gly Leu 1370 1375 1380	4242
ctc act gtg tgc tac gtg ctc act gga cga tgg gcc gat ttg gaa ctg Leu Thr Val Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu Leu 1385 1390 1395	4290

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gag aga gca gcc gat gtc aaa tgg gaa gac cag gca gag ata tca gga Glu Arg Ala Ala Asp Val Lys Trp Glu Asp Gln Ala Glu Ile Ser Gly 1400 1405 1410	4338
agc agt cca atc ctg tca ata aca ata tca gaa gat ggt agc atg tcg Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser Glu Asp Gly Ser Met Ser 1415 1420 1425 1430	4386
ata aaa aat gaa gag gaa gaa caa aca ctg acc ata ctc att aga aca Ile Lys Asn Glu Glu Glu Glu Gln Thr Leu Thr Ile Leu Ile Arg Thr 1435 1440 1445	4434
gga ttg ctg gtg atc tca gga ctt ttt cct gta tca ata cca atc acg Gly Leu Leu Val Ile Ser Gly Leu Phe Pro Val Ser Ile Pro Ile Thr 1450 1455 1460	4482
gca gca gca tgg tac ctg tgg gaa gtg aag aaa caa cgg gcc gga gta Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys Lys Gln Arg Ala Gly Val 1465 1470 1475	4530
ttg tgg gat gtt cct tca ccc cca ccc atg gga aag gct gaa ctg gaa Leu Trp Asp Val Pro Ser Pro Pro Pro Met Gly Lys Ala Glu Leu Glu 1480 1485 1490	4578
gat gga gcc tat aga att aag caa aaa ggg att ctt gga tat tcc cag Asp Gly Ala Tyr Arg Ile Lys Gln Lys Gly Ile Leu Gly Tyr Ser Gln 1495 1500 1505 1510	4626
atc gga gcc gga gtt tac aaa gaa gga aca ttc cat aca atg tgg cat Ile Gly Ala Gly Val Tyr Lys Glu Gly Thr Phe His Thr Met Trp His 1515 1520 1525	4674
gtc aca cgt ggc gct gtt cta atg cat aaa gga aag agg att gaa cca Val Thr Arg Gly Ala Val Leu Met His Lys Gly Lys Arg Ile Glu Pro 1530 1535 1540	4722
tca tgg gcg gac gtc aag aaa gac cta ata tca tat gga gga ggc tgg Ser Trp Ala Asp Val Lys Lys Asp Leu Ile Ser Tyr Gly Gly Trp 1545 1550 1555	4770
aag tta gaa gga gaa tgg aag gaa gga gaa gaa gtc cag gta ttg gca Lys Leu Glu Gly Glu Trp Lys Glu Gly Glu Glu Val Gln Val Leu Ala 1560 1565 1570	4818
ctg gag cct gga aaa aat cca aga gcc gtc caa acg aaa cct ggt ctt Leu Glu Pro Gly Lys Asn Pro Arg Ala Val Gln Thr Lys Pro Gly Leu 1575 1580 1585 1590	4866
ttc aaa acc aac gcc gga aca ata ggt gct gta tct ctg gac ttt tct Phe Lys Thr Asn Ala Gly Thr Ile Gly Ala Val Ser Leu Asp Phe Ser 1595 1600 1605	4914

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cct gga acg tca gga tct cca att atc gac aaa aaa gga aaa gtt gtg Pro Gly Thr Ser Gly Ser Pro Ile Ile Asp Lys Lys Gly Lys Val Val 1610 1615 1620	4962
ggt ctt tat ggt aat ggt gtt gtt aca agg agt gga gca tat gtg agt Gly Leu Tyr Gly Asn Gly Val Val Thr Arg Ser Gly Ala Tyr Val Ser 1625 1630 1635	5010
gct ata gcc cag act gaa aaa agc att gaa gac aac cca gag atc gaa Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile Glu 1640 1645 1650	5058
gat gac att ttc cga aag aga aga ctg acc atc atg gac ctc cac cca Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu His Pro 1655 1660 1665 1670	5106
gga gcg gga aag acg aag aga tac ctt ccg gcc ata gtc aga gaa gct Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro Ala Ile Val Arg Glu Ala 1675 1680 1685	5154
ata aaa cgg ggt ttg aga aca tta atc ttg gcc ccc act aga gtt gtg Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro Thr Arg Val Val 1690 1695 1700	5202
gca gct gaa atg gag gaa gcc ctt aga gga ctt cca ata aga tac cag Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu Pro Ile Arg Tyr Gln 1705 1710 1715	5250
acc cca gcc atc aga gct gtg cac acc ggg cgg gag att gtg gac cta Thr Pro Ala Ile Arg Ala Val His Thr Gly Arg Glu Ile Val Asp Leu 1720 1725 1730	5298
atg tgt cat gcc aca ttt acc atg agg ctg cta tca cca gtt aga gtg Met Cys His Ala Thr Phe Thr Met Arg Leu Leu Ser Pro Val Arg Val 1735 1740 1745 1750	5346
cca aac tac aac ctg att atc atg gac gaa gcc cat ttc aca gac cca Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu Ala His Phe Thr Asp Pro 1755 1760 1765	5394
gca agt ata gca gct aga gga tac atc tca act cga gtg gag atg ggt Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Glu Met Gly 1770 1775 1780	5442
gag gca gct ggg att ttt atg aca gcc act ccc ccg gga agc aga gac Glu Ala Ala Gly Ile Phe Met Thr Ala Thr Pro Pro Gly Ser Arg Asp 1785 1790 1795	5490
cca ttt cct cag agc aat gca cca atc ata gat gaa gaa aga gaa atc Pro Phe Pro Gln Ser Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu Ile 1800 1805 1810	5538
cct gaa cgc tcg tgg aat tcc gga cat gaa tgg gtc acg gat ttt aaa Pro Glu Arg Ser Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe Lys 1815 1820 1825 1830	5586

180

ggg aag act gtt tgg ttc gtt cca agt ata aaa gca gga aat gat ata Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile 1835 1840 1845	5634
gca gct tgc ctg agg aaa aat gga aag aaa gtg ata caa ctc agt agg Ala Ala Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg 1850 1855 1860	5682
aag acc ttt gat tct gag tat gtc aag act aga acc aat gat tgg gac Lys Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp 1865 1870 1875	5730
ttc gtg gtt aca act gac att tca gaa atg ggt gcc aat ttc aag gct Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys Ala 1880 1885 1890	5778
gag agg gtt ata gac ccc aga cgc tgc atg aaa cca gtc ata cta aca Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile Leu Thr 1895 1900 1905 1910	5826
gat ggt gaa gag cgg gtg att ctg gca gga cct atg cca gtg acc cac Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr His 1915 1920 1925	5874
tct agt gca gca caa aga aga ggg aga ata gga aga aat cca aaa aat Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro Lys Asn 1930 1935 1940	5922
gag aat gac cag tac ata tac atg ggg gaa cct ctg gaa aat gat gaa Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro Leu Glu Asn Asp Glu 1945 1950 1955	5970
gac tgt gca cac tgg aaa gaa gct aaa atg ctc cta gat aac atc aac Asp Cys Ala His Trp Lys Glu Ala Lys Met Leu Leu Asp Asn Ile Asn 1960 1965 1970	6018
acg cca gaa gga atc att cct agc atg ttc gaa cca gag cgt gaa aag Thr Pro Glu Gly Ile Ile Pro Ser Met Phe Glu Pro Glu Arg Glu Lys 1975 1980 1985 1990	6066
gtg gat gcc att gat ggc gaa tac cgc ttg aga gga gaa gca agg aaa Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu Arg Gly Glu Ala Arg Lys 1995 2000 2005	6114
acc ttt gta gac tta atg aga aga gga gac cta cca gtc tgg ttg gcc Thr Phe Val Asp Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ala 2010 2015 2020	6162
tac aga gtg gca gct gaa ggc atc aac tac gca gac aga agg tgg tgt Tyr Arg Val Ala Ala Glu Gly Ile Asn Tyr Ala Asp Arg Arg Trp Cys 2025 2030 2035	6210

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ttt gat gga gtc aag aac aac caa atc cta gaa gaa aac gtg gaa gtt Phe Asp Gly Val Lys Asn Asn Gln Ile Leu Glu Glu Asn Val Glu Val 2040 2045 2050	6258
gaa atc tgg aca aaa gaa ggg gaa agg aag aaa ttg aaa ccc aga tgg Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp 2055 2060 2065 2070	6306
ttg gat gct agg atc tat tct gac cca ctg gcg cta aaa gaa ttt aag Leu Asp Ala Arg Ile Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys 2075 2080 2085	6354
gaa ttt gca gcc gga aga aag tct ctg acc ctg aac cta atc aca gaa Glu Phe Ala Ala Gly Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu 2090 2095 2100	6402
atg ggt agg ctc cca acc ttc atg act cag aag gca aga gac gca ctg Met Gly Arg Leu Pro Thr Phe Met Thr Gln Lys Ala Arg Asp Ala Leu 2105 2110 2115	6450
gac aac tta gca gtg ctg cac acg gct gag gca ggt gga agg gcg tac Asp Asn Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala Tyr 2120 2125 2130	6498
aac cat gct ctc agt gaa ctg ccg gag acc ctg gag aca ttg ctt tta Asn His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu Leu Leu 2135 2140 2145 2150	6546
ctg aca ctt ctg gct aca gtc acg gga ggg atc ttt tta ttc ttg atg Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu Phe Leu Met 2155 2160 2165	6594
agc gca agg gcc ata ggg aag atg acc ctg gga atg tgc tgc ata atc Ser Ala Arg Gly Ile Gly Lys Met Thr Leu Gly Met Cys Cys Ile Ile 2170 2175 2180	6642
acg gct agc atc ctc cta tgg tac gca caa ata cag cca cac tgg ata Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln Ile Gln Pro His Trp Ile 2185 2190 2195	6690
gca gct tca ata ata ctg gag ttt ttt ctc ata gtt ttg ctt att cca Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Ile Val Leu Leu Ile Pro 2200 2205 2210	6738
gaa cct gaa aaa cag aga aca ccc caa gac aac caa ctg acc tac gtt Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn Gln Leu Thr Tyr Val 2215 2220 2225 2230	6786
gtc ata gcc atc ctc aca gtg gtg gcc gca acc atg gca aac gag atg Val Ile Ala Ile Leu Thr Val Val Ala Ala Thr Met Ala Asn Glu Met 2235 2240 2245	6834
ggt ttc cta gaa aaa acg aag aaa gat ctc gga ttg gga agc att gca Gly Phe Leu Glu Lys Thr Lys Lys Asp Leu Gly Leu Gly Ser Ile Ala 2250 2255 2260	6882

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acc cag caa ccc gag agc aac atc ctg gac ata gat cta cgt cct gca Thr Gln Gln Pro Glu Ser Asn Ile Leu Asp Ile Asp Leu Arg Pro Ala 2265 2270 2275	6930
tca gca tgg acg ctg tat gcc gtg gcc aca aca ttt gtt aca cca atg Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Phe Val Thr Pro Met 2280 2285 2290	6978
ttg aga cat agc att gaa aat tcc tca gtg aat gtg tcc cta aca gct Leu Arg His Ser Ile Glu Asn Ser Ser Val Asn Val Ser Leu Thr Ala 2295 2300 2305 2310	7026
ata gcc aac caa gcc aca gtg tta atg ggt ctc ggg aaa gga tgg cca Ile Ala Asn Gln Ala Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro 2315 2320 2325	7074
ttg tca aag atg gac atc gga gtt ccc ctt ctc gcc att gga tgc tac Leu Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala Ile Gly Cys Tyr 2330 2335 2340	7122
tca caa gtc aac ccc ata act ctc aca gca gct ctt ttc tta ttg gta Ser Gln Val Asn Pro Ile Thr Leu Thr Ala Ala Leu Phe Leu Leu Val 2345 2350 2355	7170
gca cat tat gcc atc ata ggg cca gga ctc caa gca aaa gca acc aga Ala His Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg 2360 2365 2370	7218
gaa gct cag aaa aga gca gcg gcg ggc atc atg aaa aac cca act gtc Glu Ala Gln Lys Arg Ala Ala Ala Gly Ile Met Lys Asn Pro Thr Val 2375 2380 2385 2390	7266
gat gga ata aca gtg att gac cta gat cca ata cct tat gat cca aag Asp Gly Ile Thr Val Ile Asp Leu Asp Pro Ile Pro Tyr Asp Pro Lys 2395 2400 2405	7314
ttt gaa aag cag ttg gga caa gta atg ctc cta gtc ctc tgc gtg act Phe Glu Lys Gln Leu Gly Gln Val Met Leu Leu Val Leu Cys Val Thr 2410 2415 2420	7362
caa gta ttg atg atg agg act aca tgg gct ctg tgt gag gct tta acc Gln Val Leu Met Met Arg Thr Thr Trp Ala Leu Cys Glu Ala Leu Thr 2425 2430 2435	7410
tta gct acc ggg ccc atc tcc aca ttg tgg gaa gga aat cca ggg agg Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp Glu Gly Asn Pro Gly Arg 2440 2445 2450	7458
ttt tgg aac act acc att gcg gtg tca atg gct aac att ttt aga ggg Phe Trp Asn Thr Thr Ile Ala Val Ser Met Ala Asn Ile Phe Arg Gly 2455 2460 2465 2470	7506

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agt tac ttg gcc gga gct gga ctt ctc ttt tct att atg aag aac aca Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe Ser Ile Met Lys Asn Thr 2475 2480 2485	7554
acc aac aca aga agg gga act ggc aac ata gga gag acg ctt gga gag Thr Asn Thr Arg Arg Gly Thr Gly Asn Ile Gly Glu Thr Leu Gly Glu 2490 2495 2500	7602
aaa tgg aaa agc cga ttg aac gca ttg gga aaa agt gaa ttc cag atc Lys Trp Lys Ser Arg Leu Asn Ala Leu Gly Lys Ser Glu Phe Gln Ile 2505 2510 2515	7650
tac aag aaa agt gga atc cag gaa gtg gat aga acc tta gca aaa gaa Tyr Lys Lys Ser Gly Ile Gln Glu Val Asp Arg Thr Leu Ala Lys Glu 2520 2525 2530	7698
ggc att aaa aga gga gaa acg gac cat cac gct gtg tgg cga ggc tca Gly Ile Lys Arg Gly Glu Thr Asp His His Ala Val Ser Arg Gly Ser 2535 2540 2545 2550	7746
gca aaa ctg aga tgg ttc gtt gag aga aac atg gtc aca cca gaa ggg Ala Lys Leu Arg Trp Phe Val Glu Arg Asn Met Val Thr Pro Glu Gly 2555 2560 2565	7794
aaa gta gtg gac ctc ggt tgt ggc aga gga ggc tgg tca tac tat tgt Lys Val Val Asp Leu Gly Cys Gly Arg Gly Gly Trp Ser Tyr Tyr Cys 2570 2575 2580	7842
gga gga cta aag aat gta aga gaa gtc aaa ggc cta aca aaa gga gga Gly Gly Leu Lys Asn Val Arg Glu Val Lys Gly Leu Thr Lys Gly Gly 2585 2590 2595	7890
cca gga cac gaa gaa ccc atc ccc atg tca aca tat ggg tgg aat cta Pro Gly His Glu Glu Pro Ile Pro Met Ser Thr Tyr Gly Trp Asn Leu 2600 2605 2610	7938
gtg cgt ctt caa agt gga gtt gac gtt ttc ttc atc ccg cca gaa aag Val Arg Leu Gln Ser Gly Val Asp Val Phe Ile Pro Pro Glu Lys 2615 2620 2625 2630	7986
tgt gac aca tta ttg tgt gac ata ggg gag tca tca cca aat ccc aca Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro Thr 2635 2640 2645	8034
gtg gaa gca gga cga aca ctc aga gtc ctt aac tta gta gaa aat tgg Val Glu Ala Gly Arg Thr Leu Arg Val Leu Asn Leu Val Glu Asn Trp 2650 2655 2660	8082
ttg aac aac aac act caa ttt tgc ata aag gtt ctc aac cca tat atg Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys Val Leu Asn Pro Tyr Met 2665 2670 2675	8130
ccc tca gtc ata gaa aaa atg gaa gca cta caa agg aaa tat gga gga Pro Ser Val Ile Glu Lys Met Glu Ala Leu Gln Arg Lys Tyr Gly Gly 2680 2685 2690	8178

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gcc tta gtg agg aat cca ctc tca cga aac tcc aca cat gag atg tac Ala Leu Val Arg Asn Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr 2695 2700 2705 2710	8226
tgg gta tcc aat gct tcc ggg aac ata gtg tca tca gtg aac atg att Trp Val Ser Asn Ala Ser Gly Asn Ile Val Ser Ser Val Asn Met Ile 2715 2720 2725	8274
tca agg atg ttg atc aac aga ttt aca atg aga tac aag aaa gcc act Ser Arg Met Leu Ile Asn Arg Phe Thr Met Arg Tyr Lys Lys Ala Thr 2730 2735 2740	8322
tac gag ccg gat gtt gac ctc gga agc gga acc cgt aac atc ggg att Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly Thr Arg Asn Ile Gly Ile 2745 2750 2755	8370
gaa agt gag ata cca aac cta gat ata att ggg aaa aga ata gaa aaa Glu Ser Glu Ile Pro Asn Leu Asp Ile Ile Gly Lys Arg Ile Glu Lys 2760 2765 2770	8418
ata aag caa gag cat gaa aca tca tgg cac tat gac caa gac cac cca Ile Lys Gln Glu His Glu Thr Ser Trp His Tyr Asp Gln Asp His Pro 2775 2780 2785 2790	8466
tac aaa acg tgg gca tac cat ggt agc tat gaa aca aaa cag act gga Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly 2795 2800 2805	8514
tca gca tca tcc atg gtc aac gga gtg gtc agg ctg ctg aca aaa cct Ser Ala Ser Ser Met Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro 2810 2815 2820	8562
tgg gac gtt gtc ccc atg gtg aca cag atg gca atg aca gac acg act Trp Asp Val Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr 2825 2830 2835	8610
cca ttt gga caa cag cgc gtt ttt aaa gag aaa gtg gac acg aga acc Pro Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr 2840 2845 2850	8658
caa gaa ccg aaa gaa ggc acg aag aaa cta atg aaa ata aca gca gag Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu Met Lys Ile Thr Ala Glu 2855 2860 2865 2870	8706
tgg ctt tgg aaa gaa tta ggg aag aaa aag aca ccc agg atg tgc acc Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys Thr Pro Arg Met Cys Thr 2875 2880 2885	8754
aga gaa gaa ttc aca aga aag gtg aga agc aat gca gcc ttg ggg gcc Arg Glu Glu Phe Thr Arg Lys Val Arg Ser Asn Ala Ala Leu Gly Ala 2890 2895 2900	8802

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ata ttc act gat gag aac aag tgg aag tgg gca cgt gag gct gtt gaa Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser Ala Arg Glu Ala Val Glu 2905 2910 2915	8850
gat agt agg ttt tgg gag ctg gtt gac aag gaa agg aat ctc cat ctt Asp Ser Arg Phe Trp Glu Leu Val Asp Lys Glu Arg Asn Leu His Leu 2920 2925 2930	8898
gaa gga aag tgt gaa aca tgt gtg tac aac atg atg gga aaa aga gag Glu Gly Lys Cys Glu Thr Cys Val Tyr Asn Met Met Gly Lys Arg Glu 2935 2940 2945 2950	8946
aag aag cta ggg gaa ttc ggc aag gca aaa ggc agc aga gcc ata tgg Lys Lys Leu Gly Glu Phe Gly Lys Ala Lys Gly Ser Arg Ala Ile Trp 2955 2960 2965	8994
tac atg tgg ctt gga gca cgc ttc tta gag ttt gaa gcc cta gga ttc Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu Phe Glu Ala Leu Gly Phe 2970 2975 2980	9042
tta aat gaa gat cac tgg ttc tcc aga gag aac tcc ctg agt gga gtg Leu Asn Glu Asp His Trp Phe Ser Arg Glu Asn Ser Leu Ser Gly Val 2985 2990 2995	9090
gaa gga gaa ggg ctg cac aag cta ggt tac att cta aga gac gtg agc Glu Gly Glu Gly Leu His Lys Leu Gly Tyr Ile Leu Arg Asp Val Ser 3000 3005 3010	9138
aag aaa gag gga gga gca atg tat gcc gat gac acc gca gga tgg gat Lys Lys Glu Gly Gly Ala Met Tyr Ala Asp Thr Ala Gly Trp Asp 3015 3020 3025 3030	9186
aca aga atc aca cta gaa gac cta aaa aat gaa gaa atg gta aca aac Thr Arg Ile Thr Leu Glu Asp Leu Lys Asn Glu Glu Met Val Thr Asn 3035 3040 3045	9234
cac atg gaa gga gaa cac aag aaa cta gcc gag gcc att ttc aaa cta His Met Glu Gly Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu 3050 3055 3060	9282
acg tac caa aac aag gtg gtg cgt gtg caa aga cca aca cca aga ggc Thr Tyr Gln Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly 3065 3070 3075	9330
aca gta atg gac atc ata tgg aga aga gac caa aga ggt agt gga caa Thr Val Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly Gln 3080 3085 3090	9378
gtt ggc acc tat gga ctc aat act ttc acc aat atg gaa gcc caa cta Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu 3095 3100 3105 3110	9426
atc aga cag atg gag gga gaa gga gtc ttt aaa agc att cag cac cta Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile Gln His Leu 3115 3120 3125	9474

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aca atc aca gaa gaa atc gct gtg caa aac tgg tta gca aga gtg ggg Thr Ile Thr Glu Glu Ile Ala Val Gln Asn Trp Leu Ala Arg Val Gly 3130 3135 3140	9522
cgc gaa agg tta tca aga atg gcc atc agt gga gat gat tgt gtt gtg Arg Glu Arg Leu Ser Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val 3145 3150 3155	9570
aaa cct tta gat gac agg ttc gca agc gct tta aca gct cta aat gac Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala Leu Thr Ala Leu Asn Asp 3160 3165 3170	9618
atg gga aag att agg aaa gac ata caa caa tgg gaa cct tca aga gga Met Gly Lys Ile Arg Lys Asp Ile Gln Gln Trp Glu Pro Ser Arg Gly 3175 3180 3185 3190	9666
tgg aat gat tgg aca caa gtg ccc ttc tgt tca cac cat ttc cat gag Trp Asn Asp Trp Thr Gln Val Pro Phe Cys Ser His His Phe His Glu 3195 3200 3205	9714
tta atc atg aaa gac ggt cgc gta ctc gtt gtt cca tgt aga aac caa Leu Ile Met Lys Asp Gly Arg Val Leu Val Val Pro Cys Arg Asn Gln 3210 3215 3220	9762
gat gaa ctg att ggc aga gcc cga atc tcc caa gga gca ggg tgg tct Asp Glu Leu Ile Gly Arg Ala Arg Ile Ser Gln Gly Ala Gly Trp Ser 3225 3230 3235	9810
ttg cgg gag acg gcc tgt ttg ggg aag tct tac gcc caa atg tgg agc Leu Arg Glu Thr Ala Cys Leu Gly Lys Ser Tyr Ala Gln Met Trp Ser 3240 3245 3250	9858
ttg atg tac ttc cac aga cgc gac ctc agg ctg gcg gca aat gct att Leu Met Tyr Phe His Arg Arg Asp Leu Arg Leu Ala Ala Asn Ala Ile 3255 3260 3265 3270	9906
tgc tog gca gta cca tca cat tgg gtt cca aca agt cga aca acc tgg Cys Ser Ala Val Pro Ser His Trp Val Pro Thr Ser Arg Thr Thr Trp 3275 3280 3285	9954
tcc ata cat gct aaa cat gaa tgg atg aca acg gaa gac atg ctg aca Ser Ile His Ala Lys His Glu Trp Met Thr Thr Glu Asp Met Leu Thr 3290 3295 3300	10002
gtc tgg aac agg gtg tgg att caa gaa aac cca tgg atg gaa gac aaa Val Trp Asn Arg Val Trp Ile Gln Glu Asn Pro Trp Met Glu Asp Lys 3305 3310 3315	10050
act cca gtg gaa tca tgg gag gaa atc cca tac ttg ggg aaa aga gaa Thr Pro Val Glu Ser Trp Glu Glu Ile Pro Tyr Leu Gly Lys Arg Glu 3320 3325 3330	10098

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gac caa tgg tgc ggc tca ttg att ggg tta aca agc agg gcc acc tgg 10146
 Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala Thr Trp
 3335 3340 3345 3350

gca aag aac atc caa gca gca ata aat caa gtt aga tcc ctt ata ggc 10194
 Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln Val Arg Ser Leu Ile Gly
 3355 3360 3365

aat gaa gaa tac aca gat tac atg cca tcc atg aaa aga ttc aga aga 10242
 Asn Glu Glu Tyr Thr Asp Tyr Met Pro Ser Met Lys Arg Phe Arg Arg
 3370 3375 3380

gaa gag gaa gaa gca gga gtt ctg tgg tag aaagcaaaac taacatgaaa 10292
 Glu Glu Glu Glu Ala Gly Val Leu Trp *
 3385 3390

caaggctaga agtcaggctg gattaagcca tagtacggaa aaaactatgc tacctgtgag 10352
 ccccgctcaa ggacgttaaa agaagtcagg ccatcataaa tgccatagct tgagtaaact 10412
 atgcagcctg tagctccacc tgagaagggtg taaaaaatcc gggaggccac aaacctgga 10472
 agctgtacgc atggcgtagt ggactagcgg tttagaggaga cccctccctt acaaatcgca 10532
 gcaacaatgg gggcccaagg cgagatgaag ctgtagtctc gctggaagga ctagaggtta 10592
 gaggagacc ccccgaaaaca aaaaacagca tattgacgct gggaaaagacc agagatcctg 10652
 ctgtctctc agcatcattc caggcacaga acgccagaaa atggaatggt gctgttgaat 10712
 caacaggctt c 10723

<210> 16

<211> 3391

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
 synthetic construct

<400> 16

Met Asn Asn Gln Arg Lys Lys Ala Lys Asn Thr Pro Phe Asn Met Leu
 1 5 10 15
 Lys Arg Glu Arg Asn Arg Val Ser Thr Val Gln Gln Leu Thr Lys Arg
 20 25 30
 Phe Ser Leu Gly Met Leu Gln Gly Arg Gly Pro Leu Lys Leu Phe Met
 35 40 45
 Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly
 50 55 60
 Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val
 65 70 75 80
 Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn
 85 90 95
 Arg Arg Arg Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val
 100 105 110
 Met Ala Phe His Leu Thr Thr Arg Asn Gly Glu Pro His Met Ile Val
 115 120 125
 Ser Arg Gln Glu Lys Gly Lys Ser Leu Leu Phe Lys Thr Glu Val Gly
 130 135 140

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Val	Asn	Met	Cys	Thr	Leu	Met	Ala	Met	Asp	Leu	Gly	Glu	Leu	Cys	Glu
145					150					155					160
Asp	Thr	Ile	Thr	Tyr	Lys	Cys	Pro	Leu	Leu	Arg	Gln	Asn	Glu	Pro	Glu
				165					170						175
Asp	Ile	Asp	Cys	Trp	Cys	Asn	Ser	Thr	Ser	Thr	Trp	Val	Thr	Tyr	Gly
			180					185					190		
Thr	Cys	Thr	Thr	Met	Gly	Glu	His	Arg	Arg	Glu	Lys	Arg	Ser	Val	Ala
		195					200					205			
Leu	Val	Pro	His	Val	Gly	Met	Gly	Leu	Glu	Thr	Arg	Thr	Glu	Thr	Trp
	210				215					220					
Met	Ser	Ser	Glu	Gly	Ala	Trp	Lys	His	Val	Gln	Arg	Ile	Glu	Thr	Trp
225				230						235					240
Ile	Leu	Arg	His	Pro	Gly	Phe	Thr	Met	Met	Ala	Ala	Ile	Leu	Ala	Tyr
				245					250					255	
Thr	Ile	Gly	Thr	Thr	His	Phe	Gln	Arg	Ala	Leu	Ile	Phe	Ile	Leu	Leu
			260					265					270		
Thr	Ala	Val	Thr	Pro	Ser	Met	Thr	Met	Arg	Cys	Ile	Gly	Met	Ser	Asn
	275						280					285			
Arg	Asp	Phe	Val	Glu	Gly	Val	Ser	Gly	Gly	Ser	Trp	Val	Asp	Ile	Val
290						295					300				
Leu	Glu	His	Gly	Ser	Cys	Val	Thr	Thr	Met	Ala	Lys	Asn	Lys	Pro	Thr
305					310					315					320
Leu	Asp	Phe	Glu	Leu	Ile	Lys	Thr	Glu	Ala	Lys	Gln	Pro	Ala	Thr	Leu
				325					330					335	
Arg	Lys	Tyr	Cys	Ile	Glu	Ala	Lys	Leu	Thr	Asn	Thr	Thr	Thr	Glu	Ser
		340						345					350		
Arg	Cys	Pro	Thr	Gln	Gly	Glu	Pro	Ser	Leu	Asn	Glu	Glu	Gln	Asp	Lys
		355					360					365			
Arg	Phe	Val	Cys	Lys	His	Ser	Met	Val	Asp	Arg	Gly	Trp	Gly	Asn	Gly
	370					375					380				
Cys	Gly	Leu	Phe	Gly	Lys	Gly	Gly	Ile	Val	Thr	Cys	Ala	Met	Phe	Arg
385				390						395					400
Cys	Lys	Lys	Asn	Met	Glu	Gly	Lys	Val	Val	Gln	Pro	Glu	Asn	Leu	Glu
			405						410					415	
Tyr	Thr	Ile	Val	Ile	Thr	Pro	His	Ser	Gly	Glu	Glu	His	Ala	Val	Gly
		420						425					430		
Asn	Asp	Thr	Gly	Lys	His	Gly	Lys	Glu	Ile	Lys	Ile	Thr	Pro	Gln	Ser
		435					440					445			
Ser	Ile	Thr	Glu	Ala	Glu	Leu	Thr	Gly	Tyr	Gly	Thr	Val	Thr	Met	Glu
	450					455					460				
Cys	Ser	Pro	Arg	Thr	Gly	Leu	Asp	Phe	Asn	Glu	Met	Val	Leu	Leu	Gln
465				470						475					480
Met	Glu	Asn	Lys	Ala	Trp	Leu	Val	His	Arg	Gln	Trp	Phe	Leu	Asp	Leu
			485						490					495	
Pro	Leu	Pro	Trp	Leu	Pro	Gly	Ala	Asp	Thr	Gln	Gly	Ser	Asn	Trp	Ile
		500						505					510		
Gln	Lys	Glu	Thr	Leu	Val	Thr	Phe	Lys	Asn	Pro	His	Ala	Lys	Lys	Gln
		515					520					525			
Asp	Val	Val	Val	Leu	Gly	Ser	Gln	Glu	Gly	Ala	Met	His	Thr	Ala	Leu
	530					535					540				
Thr	Gly	Ala	Thr	Glu	Ile	Gln	Met	Ser	Ser	Gly	Asn	Leu	Leu	Phe	Thr
545					550						555				560
Gly	His	Leu	Lys	Cys	Arg	Leu	Arg	Met	Asp	Lys	Leu	Gln	Leu	Lys	Gly
				565					570					575	

Met Ser Tyr Ser Met Cys Thr Gly Lys Phe Lys Val Val Lys Glu Ile
 580 585 590
 Ala Glu Thr Gln His Gly Thr Ile Val Ile Arg Val Gln Tyr Glu Gly
 595 600 605
 Asp Gly Ser Pro Cys Lys Ile Pro Phe Glu Ile Met Asp Leu Glu Lys
 610 615 620
 Arg His Val Leu Gly Arg Leu Ile Thr Val Asn Pro Ile Val Thr Glu
 625 630 635 640
 Lys Asp Ser Pro Val Asn Ile Glu Ala Glu Pro Phe Gly Asp Ser
 645 650 655
 Tyr Ile Ile Ile Gly Val Glu Pro Gly Gln Leu Lys Leu Asn Trp Phe
 660 665 670
 Lys Lys Gly Ser Ser Ile Gly Gln Met Phe Glu Thr Thr Met Arg Gly
 675 680 685
 Ala Lys Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser
 690 695 700
 Leu Gly Gly Val Phe Thr Ser Ile Gly Lys Ala Leu His Gln Val Phe
 705 710 715 720
 Gly Ala Ile Tyr Gly Ala Ala Phe Ser Gly Val Ser Trp Thr Met Lys
 725 730 735
 Ile Leu Ile Gly Val Ile Ile Thr Trp Ile Gly Met Asn Ser Arg Ser
 740 745 750
 Thr Ser Leu Ser Val Thr Leu Val Leu Val Gly Ile Val Thr Leu Tyr
 755 760 765
 Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys
 770 775 780
 Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val
 785 790 795 800
 His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys
 805 810 815
 Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile
 820 825 830
 Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro
 835 840 845
 Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met
 850 855 860
 Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg
 865 870 875 880
 Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala
 885 890 895
 Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly
 900 905 910
 Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu
 915 920 925
 Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu
 930 935 940
 Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser
 945 950 955 960
 Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp
 965 970 975
 Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe
 980 985 990
 Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser
 995 1000 1005

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Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala Gly
 1010 1015 1020
 Pro Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr
 1025 1030 1035 1040
 Gly Pro Trp His Leu Gly Lys Leu Glu Met Asp Phe Asp Phe Cys Asp
 1045 1050 1055
 Gly Thr Thr Val Val Val Thr Glu Asp Cys Gly Asn Arg Gly Pro Ser
 1060 1065 1070
 Leu Arg Thr Thr Thr Ala Ser Gly Lys Leu Ile Thr Glu Trp Cys Cys
 1075 1080 1085
 Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr Arg Gly Glu Asp Gly Cys
 1090 1095 1100
 Trp Tyr Gly Met Glu Ile Arg Pro Leu Lys Glu Lys Glu Glu Asn Leu
 1105 1110 1115 1120
 Val Asn Ser Leu Val Thr Ala Gly His Gly Gln Val Asp Asn Phe Ser
 1125 1130 1135
 Leu Gly Val Leu Gly Met Ala Leu Phe Leu Glu Glu Met Leu Arg Thr
 1140 1145 1150
 Arg Val Gly Thr Lys His Ala Ile Leu Leu Val Ala Val Ser Phe Val
 1155 1160 1165
 Thr Leu Ile Thr Gly Asn Met Ser Phe Arg Asp Leu Gly Arg Val Met
 1170 1175 1180
 Val Met Val Gly Ala Thr Met Thr Asp Asp Ile Gly Met Gly Val Thr
 1185 1190 1195 1200
 Tyr Leu Ala Leu Leu Ala Ala Phe Lys Val Arg Pro Thr Phe Ala Ala
 1205 1210 1215
 Gly Leu Leu Leu Arg Lys Leu Thr Ser Lys Glu Leu Met Met Thr Thr
 1220 1225 1230
 Ile Gly Ile Val Leu Leu Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu
 1235 1240 1245
 Glu Leu Thr Asp Ala Leu Ala Leu Gly Met Met Val Leu Lys Met Val
 1250 1255 1260
 Arg Asn Met Glu Lys Tyr Gln Leu Ala Val Thr Ile Met Ala Ile Leu
 1265 1270 1275 1280
 Cys Val Pro Asn Ala Val Ile Leu Gln Asn Ala Trp Lys Val Ser Cys
 1285 1290 1295
 Thr Ile Leu Ala Val Val Ser Val Ser Pro Leu Phe Leu Thr Ser Ser
 1300 1305 1310
 Gln Gln Lys Thr Asp Trp Ile Pro Leu Ala Leu Thr Ile Lys Gly Leu
 1315 1320 1325
 Asn Pro Thr Ala Ile Phe Leu Thr Thr Leu Ser Arg Thr Ser Lys Lys
 1330 1335 1340
 Arg Ser Trp Pro Leu Asn Glu Ala Ile Met Ala Val Gly Met Val Ser
 1345 1350 1355 1360
 Ile Leu Ala Ser Ser Leu Leu Lys Asn Asp Ile Pro Met Thr Gly Pro
 1365 1370 1375
 Leu Val Ala Gly Gly Leu Leu Thr Val Cys Tyr Val Leu Thr Gly Arg
 1380 1385 1390
 Ser Ala Asp Leu Glu Leu Glu Arg Ala Ala Asp Val Lys Trp Glu Asp
 1395 1400 1405
 Gln Ala Glu Ile Ser Gly Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser
 1410 1415 1420
 Glu Asp Gly Ser Met Ser Ile Lys Asn Glu Glu Glu Glu Gln Thr Leu
 1425 1430 1435 1440

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Thr Ile Leu Ile Arg Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro
 1445 1450 1455
 Val Ser Ile Pro Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys
 1460 1465 1470
 Lys Gln Arg Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Met
 1475 1480 1485
 Gly Lys Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys Gly
 1490 1495 1500
 Ile Leu Gly Tyr Ser Gln Ile Gly Ala Gly Val Tyr Lys Glu Gly Thr
 1505 1510 1515 1520
 Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu Met His Lys
 1525 1530 1535
 Gly Lys Arg Ile Glu Pro Ser Trp Ala Asp Val Lys Lys Asp Leu Ile
 1540 1545 1550
 Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu Trp Lys Glu Gly Glu
 1555 1560 1565
 Glu Val Gln Val Leu Ala Leu Glu Pro Gly Lys Asn Pro Arg Ala Val
 1570 1575 1580
 Gln Thr Lys Pro Gly Leu Phe Lys Thr Asn Ala Gly Thr Ile Gly Ala
 1585 1590 1595 1600
 Val Ser Leu Asp Phe Ser Pro Gly Thr Ser Gly Ser Pro Ile Ile Asp
 1605 1610 1615
 Lys Lys Gly Lys Val Val Gly Leu Tyr Gly Asn Gly Val Val Thr Arg
 1620 1625 1630
 Ser Gly Ala Tyr Val Ser Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu
 1635 1640 1645
 Asp Asn Pro Glu Ile Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr
 1650 1655 1660
 Ile Met Asp Leu His Pro Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro
 1665 1670 1675 1680
 Ala Ile Val Arg Glu Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu
 1685 1690 1695
 Ala Pro Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly
 1700 1705 1710
 Leu Pro Ile Arg Tyr Gln Thr Pro Ala Ile Arg Ala Val His Thr Gly
 1715 1720 1725
 Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg Leu
 1730 1735 1740
 Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu
 1745 1750 1755 1760
 Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser
 1765 1770 1775
 Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe Met Thr Ala Thr
 1780 1785 1790
 Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser Asn Ala Pro Ile Ile
 1795 1800 1805
 Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser Trp Asn Ser Gly His Glu
 1810 1815 1820
 Trp Val Thr Asp Phe Lys Gly Lys Thr Val Trp Phe Val Pro Ser Ile
 1825 1830 1835 1840
 Lys Ala Gly Asn Asp Ile Ala Ala Cys Leu Arg Lys Asn Gly Lys Lys
 1845 1850 1855
 Val Ile Gln Leu Ser Arg Lys Thr Phe Asp Ser Glu Tyr Val Lys Thr
 1860 1865 1870

Arg Thr Asn Asp Trp Asp Phe Val Val Thr Thr Asp Ile Ser Glu Met
 1875 1880 1885
 Gly Ala Asn Phe Lys Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met
 1890 1895 1900
 Lys Pro Val Ile Leu Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly
 1905 1910 1915 1920
 Pro Met Pro Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile
 1925 1930 1935
 Gly Arg Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu
 1940 1945 1950
 Pro Leu Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met
 1955 1960 1965
 Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met Phe
 1970 1975 1980
 Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu
 1985 1990 1995 2000
 Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg Arg Gly Asp
 2005 2010 2015
 Leu Pro Val Trp Leu Ala Tyr Arg Val Ala Ala Glu Gly Ile Asn Tyr
 2020 2025 2030
 Ala Asp Arg Arg Trp Cys Phe Asp Gly Val Lys Asn Asn Gln Ile Leu
 2035 2040 2045
 Glu Glu Asn Val Glu Val Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys
 2050 2055 2060
 Lys Leu Lys Pro Arg Trp Leu Asp Ala Arg Ile Tyr Ser Asp Pro Leu
 2065 2070 2075 2080
 Ala Leu Lys Glu Phe Lys Glu Phe Ala Ala Gly Arg Lys Ser Leu Thr
 2085 2090 2095
 Leu Asn Leu Ile Thr Glu Met Gly Arg Leu Pro Thr Phe Met Thr Gln
 2100 2105 2110
 Lys Ala Arg Asp Ala Leu Asp Asn Leu Ala Val Leu His Thr Ala Glu
 2115 2120 2125
 Ala Gly Gly Arg Ala Tyr Asn His Ala Leu Ser Glu Leu Pro Glu Thr
 2130 2135 2140
 Leu Glu Thr Leu Leu Leu Thr Leu Leu Ala Thr Val Thr Gly Gly
 2145 2150 2155 2160
 Ile Phe Leu Phe Leu Met Ser Ala Arg Gly Ile Gly Lys Met Thr Leu
 2165 2170 2175
 Gly Met Cys Cys Ile Ile Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln
 2180 2185 2190
 Ile Gln Pro His Trp Ile Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu
 2195 2200 2205
 Ile Val Leu Leu Ile Pro Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp
 2210 2215 2220
 Asn Gln Leu Thr Tyr Val Val Ile Ala Ile Leu Thr Val Val Ala Ala
 2225 2230 2235 2240
 Thr Met Ala Asn Glu Met Gly Phe Leu Glu Lys Thr Lys Lys Asp Leu
 2245 2250 2255
 Gly Leu Gly Ser Ile Ala Thr Gln Gln Pro Glu Ser Asn Ile Leu Asp
 2260 2265 2270
 Ile Asp Leu Arg Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr
 2275 2280 2285
 Thr Phe Val Thr Pro Met Leu Arg His Ser Ile Glu Asn Ser Ser Val
 2290 2295 2300

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Asn Val Ser Leu Thr Ala Ile Ala Asn Gln Ala Thr Val Leu Met Gly
 2305 2310 2315 2320
 Leu Gly Lys Gly Trp Pro Leu Ser Lys Met Asp Ile Gly Val Pro Leu
 2325 2330 2335
 Leu Ala Ile Gly Cys Tyr Ser Gln Val Asn Pro Ile Thr Leu Thr Ala
 2340 2345 2350
 Ala Leu Phe Leu Leu Val Ala His Tyr Ala Ile Ile Gly Pro Gly Leu
 2355 2360 2365
 Gln Ala Lys Ala Thr Arg Glu Ala Gln Lys Arg Ala Ala Ala Gly Ile
 2370 2375 2380
 Met Lys Asn Pro Thr Val Asp Gly Ile Thr Val Ile Asp Leu Asp Pro
 2385 2390 2395 2400
 Ile Pro Tyr Asp Pro Lys Phe Glu Lys Gln Leu Gly Gln Val Met Leu
 2405 2410 2415
 Leu Val Leu Cys Val Thr Gln Val Leu Met Met Arg Thr Thr Trp Ala
 2420 2425 2430
 Leu Cys Glu Ala Leu Thr Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp
 2435 2440 2445
 Glu Gly Asn Pro Gly Arg Phe Trp Asn Thr Thr Ile Ala Val Ser Met
 2450 2455 2460
 Ala Asn Ile Phe Arg Gly Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe
 2465 2470 2475 2480
 Ser Ile Met Lys Asn Thr Thr Asn Thr Arg Arg Gly Thr Gly Asn Ile
 2485 2490 2495
 Gly Glu Thr Leu Gly Glu Lys Trp Lys Ser Arg Leu Asn Ala Leu Gly
 2500 2505 2510
 Lys Ser Glu Phe Gln Ile Tyr Lys Lys Ser Gly Ile Gln Glu Val Asp
 2515 2520 2525
 Arg Thr Leu Ala Lys Glu Gly Ile Lys Arg Gly Glu Thr Asp His His
 2530 2535 2540
 Ala Val Ser Arg Gly Ser Ala Lys Leu Arg Trp Phe Val Glu Arg Asn
 2545 2550 2555 2560
 Met Val Thr Pro Glu Gly Lys Val Val Asp Leu Gly Cys Gly Arg Gly
 2565 2570 2575
 Gly Trp Ser Tyr Tyr Cys Gly Gly Leu Lys Asn Val Arg Glu Val Lys.
 2580 2585 2590
 Gly Leu Thr Lys Gly Gly Pro Gly His Glu Glu Pro Ile Pro Met Ser
 2595 2600 2605
 Thr Tyr Gly Trp Asn Leu Val Arg Leu Gln Ser Gly Val Asp Val Phe
 2610 2615 2620
 Phe Ile Pro Pro Glu Lys Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu
 2625 2630 2635 2640
 Ser Ser Pro Asn Pro Thr Val Glu Ala Gly Arg Thr Leu Arg Val Leu
 2645 2650 2655
 Asn Leu Val Glu Asn Trp Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys
 2660 2665 2670
 Val Leu Asn Pro Tyr Met Pro Ser Val Ile Glu Lys Met Glu Ala Leu
 2675 2680 2685
 Gln Arg Lys Tyr Gly Gly Ala Leu Val Arg Asn Pro Leu Ser Arg Asn
 2690 2695 2700
 Ser Thr His Glu Met Tyr Trp Val Ser Asn Ala Ser Gly Asn Ile Val
 2705 2710 2715 2720
 Ser Ser Val Asn Met Ile Ser Arg Met Leu Ile Asn Arg Phe Thr Met
 2725 2730 2735

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Arg Tyr Lys Lys Ala Thr Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly
 2740 2745 2750
 Thr Arg Asn Ile Gly Ile Glu Ser Glu Ile Pro Asn Leu Asp Ile Ile
 2755 2760 2765
 Gly Lys Arg Ile Glu Lys Ile Lys Gln Glu His Glu Thr Ser Trp His
 2770 2775 2800
 Tyr Asp Gln Asp His Pro Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr
 2785 2790 2795
 Glu Thr Lys Gln Thr Gly Ser Ala Ser Ser Met Val Asn Gly Val Val
 2805 2810 2815
 Arg Leu Leu Thr Lys Pro Trp Asp Val Val Pro Met Val Thr Gln Met
 2820 2825 2830
 Ala Met Thr Asp Thr Thr Pro Phe Gly Gln Gln Arg Val Phe Lys Glu
 2835 2840 2845
 Lys Val Asp Thr Arg Thr Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu
 2850 2855 2860
 Met Lys Ile Thr Ala Glu Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys
 2865 2870 2875 2880
 Thr Pro Arg Met Cys Thr Arg Glu Glu Phe Thr Arg Lys Val Arg Ser
 2885 2890 2895
 Asn Ala Ala Leu Gly Ala Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser
 2900 2905 2910
 Ala Arg Glu Ala Val Glu Asp Ser Arg Phe Trp Glu Leu Val Asp Lys
 2915 2920 2925
 Glu Arg Asn Leu His Leu Glu Gly Lys Cys Glu Thr Cys Val Tyr Asn
 2930 2935 2940
 Met Met Gly Lys Arg Glu Lys Lys Leu Gly Glu Phe Gly Lys Ala Lys
 2945 2950 2955 2960
 Gly Ser Arg Ala Ile Trp Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu
 2965 2970 2975
 Phe Glu Ala Leu Gly Phe Leu Asn Glu Asp His Trp Phe Ser Arg Glu
 2980 2985 2990
 Asn Ser Leu Ser Gly Val Glu Gly Glu Gly Leu His Lys Leu Gly Tyr
 2995 3000 3005
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 3010 3015 3020
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 Glu Ala Ile Phe Lys Leu Thr Tyr Gln Asn Lys Val Val Arg Val Gln
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 3075 3080 3085
 Gln Arg Gly Ser Gly Gln Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr
 3090 3095 3100
 Asn Met Glu Ala Gln Leu Ile Arg Gln Met Glu Gly Glu Gly Val Phe
 3105 3110 3115 3120
 Lys Ser Ile Gln His Leu Thr Ile Thr Glu Glu Ile Ala Val Gln Asn
 3125 3130 3135
 Trp Leu Ala Arg Val Gly Arg Glu Arg Leu Ser Arg Met Ala Ile Ser
 3140 3145 3150
 Gly Asp Asp Cys Val Val Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala
 3155 3160 3165

195

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Leu Thr Ala Leu Asn Asp Met Gly Lys Ile Arg Lys Asp Ile Gln Gln
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Trp Glu Pro Ser Arg Gly Trp Asn Asp Trp Thr Gln Val Pro Phe Cys
3185                3190                3195                3200
Ser His His Phe His Glu Leu Ile Met Lys Asp Gly Arg Val Leu Val
    3205                3210                3215
Val Pro Cys Arg Asn Gln Asp Glu Leu Ile Gly Arg Ala Arg Ile Ser
    3220                3225                3230
Gln Gly Ala Gly Trp Ser Leu Arg Glu Thr Ala Cys Leu Gly Lys Ser
    3235                3240                3245
Tyr Ala Gln Met Trp Ser Leu Met Tyr Phe His Arg Arg Asp Leu Arg
    3250                3255                3260
Leu Ala Ala Asn Ala Ile Cys Ser Ala Val Pro Ser His Trp Val Pro
3265                3270                3275                3280
Thr Ser Arg Thr Thr Trp Ser Ile His Ala Lys His Glu Trp Met Thr
    3285                3290                3295
Thr Glu Asp Met Leu Thr Val Trp Asn Arg Val Trp Ile Gln Glu Asn
    3300                3305                3310
Pro Trp Met Glu Asp Lys Thr Pro Val Glu Ser Trp Glu Glu Ile Pro
    3315                3320                3325
Tyr Leu Gly Lys Arg Glu Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu
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Thr Ser Arg Ala Thr Trp Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln
3345                3350                3355                3360
Val Arg Ser Leu Ile Gly Asn Glu Glu Tyr Thr Asp Tyr Met Pro Ser
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<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<221> CDS

<222> (97)...(10305)

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                               Met Asn Asn Gln Arg Lys
                               1                5

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aag gcg aaa aac acg cct ttc aat atg ctg aaa cgc gag aga aac cgc      162
Lys Ala Lys Asn Thr Pro Phe Asn Met Leu Lys Arg Glu Arg Asn Arg
    10                15                20

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    25                30                35

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196

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cgt ttc cta aca atc cca cca aca gca ggg ata ttg aag aga tgg gga Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly Ile Leu Lys Arg Trp Gly 55 60 65 70	306
aca att aaa aaa tca aaa gct att aat gtt ttg aga ggg ttc agg aaa Thr Ile Lys Lys Ser Lys Ala Ile Asn Val Leu Arg Gly Phe Arg Lys 75 80 85	354
gag att gga agg atg ctg aac atc ttg aat agg aga cgc aga tcc gcg Glu Ile Gly Arg Met Leu Asn Ile Leu Asn Arg Arg Arg Arg Ser Ala 90 95 100	402
ggc acc gga att gca gtc atg att ggc ctg atc gcc agc gta gga gca Gly Thr Gly Ile Ala Val Met Ile Gly Leu Ile Ala Ser Val Gly Ala 105 110 115	450
gtt acc ctc tct aac ttc caa ggg aag gtg atg atg acg gta aat gct Val Thr Leu Ser Asn Phe Gln Gly Lys Val Met Met Thr Val Asn Ala 120 125 130	498
act gac gtc aca gat gtc atc acg att cca aca gct gct gga aag aac Thr Asp Val Thr Asp Val Ile Thr Ile Pro Thr Ala Ala Gly Lys Asn 135 140 145 150	546
cta tgc att gtc aga gca atg gat gtg gga tac atg tgc gat gat act Leu Cys Ile Val Arg Ala Met Asp Val Gly Tyr Met Cys Asp Asp Thr 155 160 165	594
atc act tat gaa tgc cca gtg ctg tgc gct ggt aat gat cca gaa gac Ile Thr Tyr Glu Cys Pro Val Leu Ser Ala Gly Asn Asp Pro Glu Asp 170 175 180	642
atc gac tgt tgg tgc aca aag tca gca gtc tac gtc agg tat gga aga Ile Asp Cys Trp Cys Thr Lys Ser Ala Val Tyr Val Arg Tyr Gly Arg 185 190 195	690
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cag aca cac gga gaa agc act cta gcg aac aag aag ggg gct tgg atg Gln Thr His Gly Glu Ser Thr Leu Ala Asn Lys Lys Gly Ala Trp Met 215 220 225 230	786
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197

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265 270 275	
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280 285 290	
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410 415 420	
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440 445 450	
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455 460 465 470	

198

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agg aac aga gag acg tta atg gag ttt gag gaa cca cac gcc acg aag Arg Asn Arg Glu Thr Leu Met Glu Phe Glu Glu Pro His Ala Thr Lys 520 525 530	1698
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199

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200

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201

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Lys Glu Glu Asn Leu Val Asn Ser Leu Val Thr Ala Gly His Gly Gln	
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1255 1260 1265 1270	
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1275 1280 1285	
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Ile Met Ala Ile Leu Cys Val Pro Asn Ala Val Ile Leu Gln Asn Ala	
1290 1295 1300	
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Trp Lys Val Ser Cys Thr Ile Leu Ala Val Val Ser Val Ser Pro Leu	
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Leu Leu Thr Ser Ser Gln Lys Thr Asp Trp Ile Pro Leu Ala Leu	
1320 1325 1330	

202

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203

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204

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ttc gtt cca agt ata aaa gca gga aat gat ata gca gct tgc ctg agg Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile Ala Ala Cys Leu Arg 1850 1855 1860	5682
aaa aat gga aag aaa gtg ata caa ctc agt agg aag acc ttt gat tct Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg Lys Thr Phe Asp Ser 1865 1870 1875	5730
gag tat gtc aag act aga acc aat gat tgg gac ttc gtg gtt aca act Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp Phe Val Val Thr Thr 1880 1885 1890	5778
gac att tca gaa atg ggt gcc aat ttc aag gct gag agg gtt ata gac Asp Ile Ser Glu Met Gly Ala Asn Phe Lys Ala Glu Arg Val Ile Asp 1895 1900 1905 1910	5826
ccc aga cgc tgc atg aaa cca gtc ata cta aca gat ggt gaa gag cgg Pro Arg Arg Cys Met Lys Pro Val Ile Leu Thr Asp Gly Glu Glu Arg 1915 1920 1925	5874
gtg att ctg gca gga cct atg cca gtg acc cac tct agt gca gca caa Val Ile Leu Ala Gly Pro Met Pro Val Thr His Ser Ser Ala Ala Gln 1930 1935 1940	5922
aga aga ggg aga ata gga aga aat cca aaa aat gag aat gac cag tac Arg Arg Gly Arg Ile Gly Arg Asn Pro Lys Asn Glu Asn Asp Gln Tyr 1945 1950 1955	5970
ata tac atg ggg gaa cct ctg gaa aat gat gaa gac tgt gca cac tgg Ile Tyr Met Gly Glu Pro Leu Glu Asn Asp Glu Asp Cys Ala His Trp 1960 1965 1970	6018

205

aaa gaa gct aaa atg ctc cta gat aac atc aac acg cca gaa gga atc Lys Glu Ala Lys Met Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile 1975 1980 1985 1990	6066
att cct agc atg ttc gaa cca gag cgt gaa aag gtg gat gcc att gat Ile Pro Ser Met Phe Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp 1995 2000 2005	6114
ggc gaa tac cgc ttg aga gga gaa gca agg aaa acc ttt gta gac tta Gly Glu Tyr Arg Leu Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu 2010 2015 2020	6162
atg aga aga gga gac cta cca gtc tgg ttg gcc tac aga gtg gca gct Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ala Tyr Arg Val Ala Ala 2025 2030 2035	6210
gaa ggc atc aac tac gca gac aga agg tgg tgt ttt gat gga gtc aag Glu Gly Ile Asn Tyr Ala Asp Arg Arg Trp Cys Phe Asp Gly Val Lys 2040 2045 2050	6258
aac aac caa atc cta gaa gaa aac gtg gaa gtt gaa atc tgg aca aaa Asn Asn Gln Ile Leu Glu Glu Asn Val Glu Val Glu Ile Trp Thr Lys 2055 2060 2065 2070	6306
gaa ggg gaa agg aag aaa ttg aaa ccc aga tgg ttg gat gct agg atc Glu Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp Leu Asp Ala Arg Ile 2075 2080 2085	6354
tat tct gac cca ctg gcg cta aaa gaa ttt aag gaa ttt gca gcc gga Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys Glu Phe Ala Ala Gly 2090 2095 2100	6402
aga aag tct ctg acc ctg aac cta atc aca gaa atg ggt agg ctc cca Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu Met Gly Arg Leu Pro 2105 2110 2115	6450
acc ttc atg act cag aag gca aga gac gca ctg gac aac tta gca gtg Thr Phe Met Thr Gln Lys Ala Arg Asp Ala Leu Asp Asn Leu Ala Val 2120 2125 2130	6498
ctg cac acg gct gag gca ggt gga agg gcg tac aac cat gct ctc agt Leu His Thr Ala Glu Ala Gly Gly Arg Ala Tyr Asn His Ala Leu Ser 2135 2140 2145 2150	6546
gaa ctg ccg gag acc ctg gag aca ttg ctt tta ctg aca ctt ctg gct Glu Leu Pro Glu Thr Leu Glu Thr Leu Leu Leu Thr Leu Leu Ala 2155 2160 2165	6594
aca gtc acg gga ggg atc ttt tta ttc ttg atg agc gga agg ggc ata Thr Val Thr Gly Gly Ile Phe Leu Phe Leu Met Ser Gly Arg Gly Ile 2170 2175 2180	6642
ggg aag atg acc ctg gga atg tgc tgc ata atc acg gct agc atc ctc Gly Lys Met Thr Leu Gly Met Cys Cys Ile Ile Thr Ala Ser Ile Leu 2185 2190 2195	6690

206

cta tgg tac gca caa ata cag cca cac tgg ata gca gct tca ata ata Leu Trp Tyr Ala Gln Ile Gln Pro His Trp Ile Ala Ala Ser Ile Ile 2200 2205 2210	6738
ctg gag ttt ttt ctc ata gtt ttg ctt att cca gaa cct gaa aaa cag Leu Glu Phe Phe Leu Ile Val Leu Leu Ile Pro Glu Pro Glu Lys Gln 2215 2220 2225 2230	6786
aga aca ccc caa gac aac caa ctg acc tac gtt gtc ata gcc atc ctc Arg Thr Pro Gln Asp Asn Gln Leu Thr Tyr Val Val Ile Ala Ile Leu 2235 2240 2245	6834
aca gtg gtg gcc gca acc atg gca aac gag atg ggt ttc cta gaa aaa Thr Val Val Ala Ala Thr Met Ala Asn Glu Met Gly Phe Leu Glu Lys 2250 2255 2260	6882
acg aag aaa gat ctc gga ttg gga agc att gca acc cag caa ccc gag Thr Lys Lys Asp Leu Gly Leu Gly Ser Ile Ala Thr Gln Gln Pro Glu 2265 2270 2275	6930
agc aac atc ctg gac ata gat cta cgt cct gca tca gca tgg acg ctg Ser Asn Ile Leu Asp Ile Asp Leu Arg Pro Ala Ser Ala Trp Thr Leu 2280 2285 2290	6978
tat gcc gtg gcc aca aca ttt gtt aca cca atg ttg aga cat agc att Tyr Ala Val Ala Thr Thr Phe Val Thr Pro Met Leu Arg His Ser Ile 2295 2300 2305 2310	7026
gaa aat tcc tca gtg aat gtg tcc cta aca gct ata gcc aac caa gcc Glu Asn Ser Ser Val Asn Val Ser Leu Thr Ala Ile Ala Asn Gln Ala 2315 2320 2325	7074
aca gtg tta atg ggt ctc ggg aaa gga tgg cca ttg tca aag atg gac Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro Leu Ser Lys Met Asp 2330 2335 2340	7122
atc gga gtt ccc ctt ctc gcc att gga tgc tac tca caa gtc aac ccc Ile Gly Val Pro Leu Leu Ala Ile Gly Cys Tyr Ser Gln Val Asn Pro 2345 2350 2355	7170
ata act ctc aca gca gct ctt ttc tta ttg gta gca cat tat gcc atc Ile Thr Leu Thr Ala Ala Leu Phe Leu Leu Val Ala His Tyr Ala Ile 2360 2365 2370	7218
ata ggg cca gga ctc caa aaa gca acc aga gaa gct cag aaa aga Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg Glu Ala Gln Lys Arg 2375 2380 2385 2390	7266
gca gcg gcg gcc atc atg aaa aac cca act gtc gat gga ata aca gtg Ala Ala Ala Gly Ile Met Lys Asn Pro Thr Val Asp Gly Ile Thr Val 2395 2400 2405	7314

207

att gac cta gat cca ata cct tat gat cca aag ttt gaa aag cag ttg Ile Asp Leu Asp Pro Ile Pro Tyr Asp Pro Lys Phe Glu Lys Gln Leu 2410 2415 2420	7362
gga caa gta atg ctc cta gtc ctc tgc gtg act caa gta ttg atg atg Gly Gln Val Met Leu Leu Val Leu Cys Val Thr Gln Val Leu Met Met 2425 2430 2435	7410
agg act aca tgg gct ctg tgt gag gct tta acc tta gct acc ggg ccc Arg Thr Thr Trp Ala Leu Cys Glu Ala Leu Thr Leu Ala Thr Gly Pro 2440 2445 2450	7458
atc tcc aca ttg tgg gaa gga aat cca ggg agg ttt tgg aac act acc Ile Ser Thr Leu Trp Glu Gly Asn Pro Gly Arg Phe Thr Asn Thr Thr 2455 2460 2465 2470	7506
att gcg gtg tca atg gct aac att ttt aga ggg agt tac ttg gcc gga Ile Ala Val Ser Met Ala Asn Ile Phe Arg Gly Ser Tyr Leu Ala Gly 2475 2480 2485	7554
gct gga ctt ctc ttt tct att atg aag aac aca acc aac aca aga agg Ala Gly Leu Leu Phe Ser Ile Met Lys Asn Thr Thr Asn Thr Arg Arg 2490 2495 2500	7602
gga act ggc aac ata gga gag acg ctt gga gag aaa tgg aaa agc cga Gly Thr Gly Asn Ile Gly Glu Thr Leu Gly Glu Lys Trp Lys Ser Arg 2505 2510 2515	7650
ttg aac gca ttg gga aaa agt gaa ttc cag atc tac aag aaa agt gga Leu Asn Ala Leu Gly Lys Ser Glu Phe Gln Ile Tyr Lys Lys Ser Gly 2520 2525 2530	7698
atc cag gaa gtg gat aga acc tta gca aaa gaa ggc att aaa aga gga Ile Gln Glu Val Asp Arg Thr Leu Ala Lys Glu Gly Ile Lys Arg Gly 2535 2540 2545 2550	7746
gaa acg gac cat cac gct gtg tcg cga ggc tca gca aaa ctg aga tgg Glu Thr Asp His Ile Ala Val Ser Arg Gly Ser Ala Lys Leu Arg Trp 2555 2560 2565	7794
ttc gtt gag aga aac atg gtc aca cca gaa ggg aaa gta gtg gac ctc Phe Val Glu Arg Asn Met Val Thr Pro Glu Gly Lys Val Val Asp Leu 2570 2575 2580	7842
ggc tgt ggc aga gga ggc tgg tca tac tat tgt gga gga cta aag aat Gly Cys Gly Arg Gly Gly Trp Ser Tyr Tyr Cys Gly Gly Leu Lys Asn 2585 2590 2595	7890
gta aga gaa gtc aaa ggc cta aca aaa gga gga cca gga cac gaa gaa Val Arg Glu Val Lys Gly Leu Thr Lys Gly Gly Pro Gly His Glu Glu 2600 2605 2610	7938
ccc atc ccc atg tca aca tat ggg tgg aat cta gtg cgt ctt caa agt Pro Ile Pro Met Ser Thr Tyr Gly Trp Asn Leu Val Arg Leu Gln Ser 2615 2620 2625 2630	7986

208

gga gtt gac gtt ttc ttc atc ccg cca gaa aag tgt gac aca tta ttg Gly Val Asp Val Phe Phe Ile Pro Pro Glu Lys Cys Asp Thr Leu Leu 2635 2640 2645	8034
tgt gac ata ggg gag tca tca cca aat ccc aca gtg gaa gca gga cga Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro Thr Val Glu Ala Gly Arg 2650 2655 2660	8082
aca ctc aga gtc ctt aac tta gta gaa aat tgg ttg aac aac aac act Thr Leu Arg Val Leu Asn Leu Val Glu Asn Trp Leu Asn Asn Thr 2665 2670 2675	8130
caa ttt tgc ata aag gtt ctc aac cca tat atg ccc tca gtc ata gaa Gln Phe Cys Ile Lys Val Leu Asn Pro Tyr Met Pro Ser Val Ile Glu 2680 2685 2690	8178
aaa atg gaa gca cta caa agg aaa tat gga gga gcc tta gtg agg aat Lys Met Glu Ala Leu Gln Arg Lys Tyr Gly Gly Ala Leu Val Arg Asn 2695 2700 2705 2710	8226
cca ctc tca cga aac tcc aca cat gag atg tac tgg gta tcc aat gct Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr Trp Val Ser Asn Ala 2715 2720 2725	8274
tcc ggg aac ata gtg tca tca gtg aac atg att tca agg atg ttg atc Ser Gly Asn Ile Val Ser Ser Val Asn Met Ile Ser Arg Met Leu Ile 2730 2735 2740	8322
aac aga ttt aca atg aga tac aag aaa gcc act tac gag ccg gat gtt Asn Arg Phe Thr Met Arg Tyr Lys Lys Ala Thr Tyr Glu Pro Asp Val 2745 2750 2755	8370
gac ctc gga agc gga acc cgt aac atc ggg att gaa agt gag ata cca Asp Leu Gly Ser Gly Thr Arg Asn Ile Gly Ile Glu Ser Glu Ile Pro 2760 2765 2770	8418
aac cta gat ata att ggg aaa aga ata gaa aaa ata aag caa gag cat Asn Leu Asp Ile Ile Gly Lys Arg Ile Glu Lys Ile Lys Gln Glu His 2775 2780 2785 2790	8466
gaa aca tca tgg cac tat gac caa gac cac cca tac aaa acg tgg gca Glu Thr Ser Trp His Tyr Asp Gln Asp His Pro Tyr Lys Thr Trp Ala 2795 2800 2805	8514
tac cat ggt agc tat gaa aca aaa cag act gga tca gca tca tcc atg Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly Ser Ala Ser Ser Met 2810 2815 2820	8562
gtc aac gga gtg gtc agg ctg ctg aca aaa cct tgg gac gtc gtc ccc Val Asn Gly Val Val Arg Leu Leu Thr Lys Pro Trp Asp Val Val Pro 2825 2830 2835	8610

209

atg gtg aca cag atg gca atg aca gac acg act cca ttt gga caa cag Met Val Thr Gln Met Ala Met Thr Asp Thr Thr Pro Phe Gly Gln Gln 2840 2845 2850	8658
cgc gtt ttt aaa gag aaa gtg gac acg aga acc caa gaa ccg aaa gaa Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr Gln Glu Pro Lys Glu 2855 2860 2865 2870	8706
ggc acg aag aaa cta atg aaa ata aca gca gag tgg ctt tgg aaa gaa Gly Thr Lys Lys Leu Met Lys Ile Thr Ala Glu Trp Leu Trp Lys Glu 2875 2880 2885	8754
tta ggg aag aaa aag aca ccc agg atg tgc acc aga gaa gaa ttc aca Leu Gly Lys Lys Lys Thr Pro Arg Met Cys Thr Arg Glu Glu Phe Thr 2890 2895 2900	8802
aga aag gtg aga agc aat gca gcc ttg ggg gcc ata ttc act gat gag Arg Lys Val Arg Ser Asn Ala Ala Leu Gly Ala Ile Phe Thr Asp Glu 2905 2910 2915	8850
aac aag tgg aag tcg gca cgt gag gct gtt gaa gat agt agg ttt tgg Asn Lys Trp Lys Ser Ala Arg Glu Ala Val Glu Asp Ser Arg Phe Trp 2920 2925 2930	8898
gag ctg gtt gac aag gaa agg aat ctc cat ctt gaa gga aag tgt gaa Glu Leu Val Asp Lys Glu Arg Asn Leu His Leu Glu Gly Lys Cys Glu 2935 2940 2945 2950	8946
aca tgt gtg tac aac atg atg gga aaa aga gag aag aag cta ggg gaa Thr Cys Val Tyr Asn Met Met Gly Lys Arg Glu Lys Lys Leu Gly Glu 2955 2960 2965	8994
ttc ggc aag gca aaa ggc agc aga gcc ata tgg tac atg tgg ctt gga Phe Gly Lys Ala Lys Gly Ser Arg Ala Ile Trp Tyr Met Trp Leu Gly 2970 2975 2980	9042
gca cgc ttc tta gag ttt gaa gcc cta gga ttc tta aat gaa gat cac Ala Arg Phe Leu Glu Phe Glu Ala Leu Gly Phe Leu Asn Glu Asp His 2985 2990 2995	9090
tgg ttc tcc aga gag aac tcc ctg agt gga gtg gaa gga gaa ggg ctg Trp Phe Ser Arg Glu Asn Ser Leu Ser Gly Val Glu Gly Glu Gly Leu 3000 3005 3010	9138
cac aag cta ggt tac att cta aga gac gtg agc aag aaa gag gga gga His Lys Leu Gly Tyr Ile Leu Arg Asp Val Ser Lys Lys Glu Gly Gly 3015 3020 3025 3030	9186
gca atg tat gcc gat gac acc gca gga tgg gat aca aga atc aca cta Ala Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp Thr Arg Ile Thr Leu 3035 3040 3045	9234
gaa gac cta aaa aat gaa gaa atg gta aca aac cac atg gaa gga gaa Glu Asp Leu Lys Asn Glu Glu Met Val Thr Asn His Met Glu Gly Glu 3050 3055 3060	9282

210

cac aag aaa cta gcc gag gcc att ttc aaa cta acg tac caa aac aag His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu Thr Tyr Gln Asn Lys 3065 3070 3075	9330
gtg gtg cgt gtg caa aga cca aca cca aga ggc aca gta atg gac atc Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly Thr Val Met Asp Ile 3080 3085 3090	9378
ata tcg aga aga gac caa aga ggt agt gga caa gtt ggc acc tat gga Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly Gln Val Gly Thr Tyr Gly 3095 3100 3105 3110	9426
ctc aat act ttc acc aat atg gaa gcc caa cta atc aga cag atg gag Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu Ile Arg Gln Met Glu 3115 3120 3125	9474
gga gaa gga gtc ttt aaa agc att cag cac cta aca atc aca gaa gaa Gly Glu Gly Val Phe Lys Ser Ile Gln His Leu Thr Ile Thr Glu Glu 3130 3135 3140	9522
atc gct gtg caa aac tgg tta gca aga gtg ggg cgc gaa agg tta tca Ile Ala Val Gln Asn Trp Leu Ala Arg Val Gly Arg Glu Arg Leu Ser 3145 3150 3155	9570
aga atg gcc atc agt gga gat gat tgt gtt gtg aaa cct tta gat gac Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val Lys Pro Leu Asp Asp 3160 3165 3170	9618
agg ttc gca agc gct tta aca gct cta aat gac atg gga aag att agg Arg Phe Ala Ser Ala Leu Thr Ala Leu Asn Asp Met Gly Lys Ile Arg 3175 3180 3185 3190	9666
aaa gac ata caa caa tgg gaa cct tca aga gga tgg aat gat tgg aca Lys Asp Ile Gln Gln Trp Glu Pro Ser Arg Gly Trp Asn Asp Trp Thr 3195 3200 3205	9714
caa gtg ccc ttc tgt tca cac cat ttc cat gag tta atc atg aaa gac Gln Val Pro Phe Cys Ser His His Phe His Glu Leu Ile Met Lys Asp 3210 3215 3220	9762
ggc cgc gta ctc gtt gtt cca tgt aga aac caa gat gaa ctg att ggc Gly Arg Val Leu Val Val Pro Cys Arg Asn Gln Asp Glu Leu Ile Gly 3225 3230 3235	9810
aga gcc cga atc tcc caa gga gca ggg tgg tct ttg cgg gag acg gcc Arg Ala Arg Ile Ser Gln Gly Ala Gly Trp Ser Leu Arg Glu Thr Ala 3240 3245 3250	9858
tgt ttg ggg aag tct tac gcc caa atg tgg agc ttg atg tac ttc cac Cys Leu Gly Lys Ser Tyr Ala Gln Met Trp Ser Leu Met Tyr Phe His 3255 3260 3265 3270	9906

211

aga cgc gac ctc	agg ctg gcg gca aat gct att tgc tgc gca gta cca	9954
Arg Arg Asp Leu	Arg Leu Ala Ala Asn Ala Ile Cys Ser Ala Val Pro	
3275	3280 3285	
tca cat tgg gtt	cca aca agt cga aca acc tgg tcc ata cat gct aaa	10002
Ser His Trp Val	Pro Thr Ser Arg Thr Thr Trp Ser Ile His Ala Lys	
3290	3295 3300	
cat gaa tgg atg	aca acg gaa gac atg ctg aca gtc tgg aac agg gtg	10050
His Glu Trp Met	Thr Thr Glu Asp Met Leu Thr Val Trp Asn Arg Val	
3305	3310 3315	
tgg att caa gaa	aac cca tgg atg gaa gac aaa act cca gtg gaa tca	10098
Trp Ile Gln Glu	Asn Pro Trp Met Glu Asp Lys Thr Pro Val Glu Ser	
3320	3325 3330	
tgg gag gaa atc	cca tac ttg ggg aaa aga gaa gac caa tgg tgc ggc	10146
Trp Glu Glu Ile	Pro Tyr Leu Gly Lys Arg Glu Asp Gln Trp Cys Gly	
3335	3340 3345 3350	
tca ttg att ggg	tta aca agc agg gcc acc tgg gca aag aac atc caa	10194
Ser Leu Ile Gly	Leu Thr Ser Arg Ala Thr Trp Ala Lys Asn Ile Gln	
3355	3360 3365	
gca gca ata aat	caa gtt aga tcc ctt ata ggc aat gaa gaa tac aca	10242
Ala Ala Ile Asn	Gln Val Arg Ser Leu Ile Gly Asn Glu Glu Tyr Thr	
3370	3375 3380	
gat tac atg cca	tcc atg aaa aga ttc aga aga gaa gag gaa gaa gca	10290
Asp Tyr Met Pro	Ser Met Lys Arg Phe Arg Arg Glu Glu Glu Ala	
3385	3390 3395	
gga gtt ctg tgg	tag aaagcaaac taacatgaaa caaggctaga agtcaggtcg	10345
Gly Val Leu Trp	*	
3400		
gattaagcca tagtacggaa	aaaactatgc tacctgtgag ccccgctcaa ggacgttaaa	10405
agaagtcagg ccatcataaa	tgccatagct tgagtaaact atgcagcctg tagctccacc	10465
tgagaagggtg taataaaatcc	gggaggccac aaaccatgga agctgtacgc atggcgtagt	10525
ggactagcgg ttagaggaga	ccctccctt acaaatcgca gcaacaatgg gggcccaagg	10585
cgaatgaag ctgtagtctc	gctggaagga ctagaggtta gaggagacc cccgaaaca	10645
aaaaacagca tattgacgct	gggaaagacc agagatcctg ctgtctctc agcatcattc	10705
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<210> 18

<211> 3402

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<400> 18

212

Met	Asn	Asn	Gln	Arg	Lys	Lys	Ala	Lys	Asn	Thr	Pro	Phe	Asn	Met	Leu	
1				5					10					15		
Lys	Arg	Glu	Arg	Asn	Arg	Val	Ser	Thr	Val	Gln	Gln	Leu	Thr	Lys	Arg	
			20					25					30			
Phe	Ser	Leu	Gly	Met	Leu	Gln	Gly	Arg	Gly	Pro	Leu	Lys	Leu	Phe	Met	
		35					40					45				
Ala	Leu	Val	Ala	Phe	Leu	Arg	Phe	Leu	Thr	Ile	Pro	Pro	Thr	Ala	Gly	
	50					55				60						
Ile	Leu	Lys	Arg	Trp	Gly	Thr	Ile	Lys	Lys	Ser	Lys	Ala	Ile	Asn	Val	
65				70					75					80		
Leu	Arg	Gly	Phe	Arg	Lys	Glu	Ile	Gly	Arg	Met	Leu	Asn	Ile	Leu	Asn	
				85					90					95		
Arg	Arg	Arg	Arg	Ser	Ala	Gly	Thr	Gly	Ile	Ala	Val	Met	Ile	Gly	Leu	
			100					105					110			
Ile	Ala	Ser	Val	Gly	Ala	Val	Thr	Leu	Ser	Asn	Phe	Gln	Gly	Lys	Val	
	115					120						125				
Met	Met	Thr	Val	Asn	Ala	Thr	Asp	Val	Thr	Asp	Val	Ile	Thr	Ile	Pro	
130					135						140					
Thr	Ala	Ala	Gly	Lys	Asn	Leu	Cys	Ile	Val	Arg	Ala	Met	Asp	Val	Gly	
145				150						155					160	
Tyr	Met	Cys	Asp	Asp	Thr	Ile	Thr	Tyr	Glu	Cys	Pro	Val	Leu	Ser	Ala	
				165					170					175		
Gly	Asn	Asp	Pro	Glu	Asp	Ile	Asp	Cys	Trp	Cys	Thr	Lys	Ser	Ala	Val	
		180						185					190			
Tyr	Val	Arg	Tyr	Gly	Arg	Cys	Thr	Lys	Thr	Arg	His	Ser	Arg	Arg	Ser	
	195					200						205				
Arg	Arg	Ser	Leu	Thr	Val	Gln	Thr	His	Gly	Glu	Ser	Thr	Leu	Ala	Asn	
210					215						220					
Lys	Lys	Gly	Ala	Trp	Met	Asp	Ser	Thr	Lys	Ala	Thr	Arg	Tyr	Leu	Val	
225				230						235				240		
Lys	Thr	Glu	Ser	Trp	Ile	Leu	Arg	Asn	Pro	Gly	Tyr	Ala	Leu	Val	Ala	
				245					250					255		
Ala	Val	Ile	Gly	Trp	Met	Leu	Gly	Ser	Asn	Thr	Met	Gln	Arg	Val	Val	
	260							265					270			
Phe	Val	Val	Leu	Leu	Leu	Leu	Val	Ala	Pro	Ala	Tyr	Ser	Phe	Asn	Cys	
	275					280						285				
Leu	Gly	Met	Ser	Asn	Arg	Asp	Phe	Leu	Glu	Gly	Val	Ser	Gly	Ala	Thr	
290						295					300					
Trp	Val	Asp	Leu	Val	Leu	Glu	Gly	Asp	Ser	Cys	Val	Thr	Ile	Met	Ser	
305					310					315				320		
Lys	Asp	Lys	Pro	Thr	Ile	Asp	Val	Lys	Met	Met	Asn	Met	Glu	Ala	Ala	
				325					330					335		
Asn	Leu	Ala	Glu	Val	Arg	Ser	Tyr	Cys	Tyr	Leu	Ala	Thr	Val	Ser	Asp	
	340							345					350			
Leu	Ser	Thr	Lys	Ala	Ala	Cys	Pro	Thr	Met	Gly	Glu	Ala	His	Asn	Asp	
	355						360					365				
Lys	Arg	Ala	Asp	Pro	Ala	Phe	Val	Cys	Arg	Gln	Gly	Val	Val	Asp	Arg	
	370					375					380					
Gly	Trp	Gly	Asn	Gly	Cys	Gly	Leu	Phe	Gly	Lys	Gly	Ser	Ile	Asp	Thr	
385					390					395				400		
Cys	Ala	Lys	Phe	Ala	Cys	Ser	Thr	Lys	Ala	Ile	Gly	Arg	Thr	Ile	Leu	
				405					410					415		
Lys	Glu	Asn	Ile	Lys	Tyr	Glu	Val	Ala	Ile	Phe	Val	His	Gly	Pro	Thr	
	420							425					430			

213

Thr Val Glu Ser His Gly Asn Tyr Ser Thr Gln Val Gly Ala Thr Gln
 435 440 445
 Ala Gly Arg Phe Ser Ile Thr Pro Ala Ala Pro Ser Tyr Thr Leu Lys
 450 455 460
 Leu Gly Glu Tyr Gly Glu Val Thr Val Asp Cys Glu Pro Arg Ser Gly
 465 470 475 480
 Ile Asp Thr Asn Ala Tyr Tyr Val Met Thr Val Gly Thr Lys Thr Phe
 485 490 495
 Leu Val His Arg Glu Trp Phe Met Asp Leu Asn Leu Pro Trp Ser Ser
 500 505 510
 Ala Gly Ser Thr Val Trp Arg Asn Arg Glu Thr Leu Met Glu Phe Glu
 515 520 525
 Glu Pro His Ala Thr Lys Gln Ser Val Ile Ala Leu Gly Ser Gln Glu
 530 535 540
 Gly Ala Leu His Gln Ala Leu Ala Gly Ala Ile Pro Val Glu Phe Ser
 545 550 555 560
 Ser Asn Thr Val Lys Leu Thr Ser Gly His Leu Lys Cys Arg Val Lys
 565 570 575
 Met Glu Lys Leu Gln Leu Lys Gly Thr Thr Tyr Gly Val Cys Ser Lys
 580 585 590
 Ala Phe Lys Phe Leu Gly Thr Pro Ala Asp Thr Gly His Gly Thr Val
 595 600 605
 Val Leu Glu Leu Gln Tyr Thr Gly Thr Asp Gly Pro Cys Lys Val Pro
 610 615 620
 Ile Ser Ser Val Ala Ser Leu Asn Asp Leu Thr Pro Val Gly Arg Leu
 625 630 635 640
 Val Thr Val Asn Pro Phe Val Ser Val Ala Thr Ala Asn Ala Lys Val
 645 650 655
 Leu Ile Glu Leu Glu Pro Pro Phe Gly Asp Ser Tyr Ile Val Val Gly
 660 665 670
 Arg Gly Glu Gln Gln Ile Asn His His Trp His Lys Ser Gly Ser Ser
 675 680 685
 Ile Gly Lys Ala Phe Thr Thr Thr Leu Lys Gly Ala Gln Arg Leu Ala
 690 695 700
 Ala Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser Val Gly Gly Val Phe
 705 710 715 720
 Thr Ser Val Gly Lys Ala Val His Gln Val Phe Gly Gly Ala Phe Arg
 725 730 735
 Ser Leu Phe Gly Gly Met Ser Trp Ile Thr Gln Gly Leu Leu Gly Ala
 740 745 750
 Leu Leu Leu Trp Met Gly Ile Asn Ala Arg Asp Arg Ser Ile Ala Leu
 755 760 765
 Thr Phe Leu Ala Ala Gly Ile Val Thr Leu Tyr Leu Gly Val Met Val
 770 775 780
 Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys Asn Lys Glu Leu Lys
 785 790 795 800
 Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val His Thr Trp Thr Glu
 805 810 815
 Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys Leu Ala Ser Ala Ile
 820 825 830
 Gln Lys Ala His Glu Glu Gly Ile Cys Gly Ile Arg Ser Val Thr Arg
 835 840 845
 Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro Glu Leu Asn His Ile
 850 855 860

214

Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met Thr Gly Asp Ile Lys
 865 870 875 880
 Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg Pro Gln Pro Thr Glu
 885 890 895
 Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala Lys Met Leu Ser Thr
 900 905 910
 Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly Pro Glu Thr Ala Glu
 915 920 925
 Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu Glu Val Glu Asp Tyr
 930 935 940
 Gly Phe Gly Val Phe Thr Asn Ile Trp Leu Lys Leu Lys Glu Lys
 945 950 955 960
 Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser Ala Ala Ile Lys Asp
 965 970 975
 Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp Ile Glu Ser Ala Leu
 980 985 990
 Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe Ile Glu Val Lys Asn
 995 1000 1005
 Cys His Trp Pro Lys Ser His Thr Leu Trp Ser Asn Gly Val Leu Glu
 1010 1015 1020
 Ser Glu Met Ile Ile Pro Lys Asn Leu Ala Gly Pro Val Ser Gln His
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 Asn Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr Gly Pro Trp His Leu
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 Gly Lys Leu Glu Met Asp Phe Asp Phe Cys Asp Gly Thr Thr Val Val
 1060 1065 1070
 Val Thr Glu Asp Cys Gly Asn Arg Gly Pro Ser Leu Arg Thr Thr Thr
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 1090 1095 1100
 Pro Pro Leu Arg Tyr Arg Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu
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 Ile Arg Pro Leu Lys Glu Lys Glu Glu Asn Leu Val Asn Ser Leu Val
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 Thr Ala Gly His Gly Gln Val Asp Asn Phe Ser Leu Gly Val Leu Gly
 1140 1145 1150
 Met Ala Leu Phe Leu Glu Glu Met Leu Arg Thr Arg Val Gly Thr Lys
 1155 1160 1165
 His Ala Ile Leu Leu Val Ala Val Ser Phe Val Thr Leu Ile Thr Gly
 1170 1175 1180
 Asn Met Ser Phe Arg Asp Leu Gly Arg Val Met Val Met Val Gly Ala
 1185 1190 1195 1200
 Thr Met Thr Asp Asp Ile Gly Met Gly Val Thr Tyr Leu Ala Leu Leu
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 1220 1225 1230
 Lys Leu Thr Ser Lys Glu Leu Met Met Thr Thr Ile Gly Ile Val Leu
 1235 1240 1245
 Leu Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu Glu Leu Thr Asp Ala
 1250 1255 1260
 Leu Ala Leu Gly Met Met Val Leu Lys Met Val Arg Asn Met Glu Lys
 1265 1270 1275 1280
 Tyr Gln Leu Ala Val Thr Ile Met Ala Ile Leu Cys Val Pro Asn Ala
 1285 1290 1295

215

Val Ile Leu Gln Asn Ala Trp Lys Val Ser Cys Thr Ile Leu Ala Val
 1300 1305 1310
 Val Ser Val Ser Pro Leu Leu Leu Thr Ser Ser Gln Gln Lys Thr Asp
 1315 1320 1325
 Trp Ile Pro Leu Ala Leu Thr Ile Lys Gly Leu Asn Pro Thr Ala Ile
 1330 1335 1340
 Phe Leu Thr Thr Leu Ser Arg Thr Ser Lys Lys Arg Ser Trp Pro Leu
 1345 1350 1355 1360
 Asn Glu Ala Ile Met Ala Val Gly Met Val Ser Ile Leu Ala Ser Ser
 1365 1370 1375
 Leu Leu Lys Asn Asp Ile Pro Met Thr Gly Pro Leu Val Ala Gly Gly
 1380 1385 1390
 Leu Leu Thr Val Cys Tyr Val Leu Thr Gly Arg Ser Ala Asp Leu Glu
 1395 1400 1405
 Leu Glu Arg Ala Ala Asp Val Lys Trp Glu Asp Gln Ala Glu Ile Ser
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 Gly Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser Glu Asp Gly Ser Met
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 Ser Ile Lys Asn Glu Glu Glu Gln Thr Leu Thr Ile Leu Ile Arg
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 Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro Val Ser Ile Pro Ile
 1460 1465 1470
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 Val Leu Trp Asp Val Pro Ser Pro Pro Pro Met Gly Lys Ala Glu Leu
 1490 1495 1500
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 His Val Thr Arg Gly Ala Val Leu Met His Lys Gly Lys Arg Ile Glu
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 Pro Ser Trp Ala Asp Val Lys Lys Asp Leu Ile Ser Tyr Gly Gly Gly
 1555 1560 1565
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 Ser Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu Asp Asn Pro Glu Ile
 1650 1655 1660
 Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr Ile Met Asp Leu His
 1665 1670 1675 1680
 Pro Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro Ala Ile Val Arg Glu
 1685 1690 1695
 Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu Ala Pro Thr Arg Val
 1700 1705 1710
 Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu Pro Ile Arg Tyr
 1715 1720 1725

216

Gln Thr Pro Ala Ile Arg Ala Glu His Thr Gly Arg Glu Ile Val Asp
 1730 1735 1740
 Leu Met Cys His Ala Thr Phe Thr Met Arg Leu Leu Ser Pro Val Arg
 1745 1750 1755 1760
 Val Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu Ala His Phe Thr Asp
 1765 1770 1775
 Pro Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Glu Met
 1780 1785 1790
 Gly Glu Ala Ala Gly Ile Phe Met Thr Ala Thr Pro Pro Gly Ser Arg
 1795 1800 1805
 Asp Pro Phe Pro Gln Ser Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu
 1810 1815 1820
 Ile Pro Glu Arg Ser Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe
 1825 1830 1835 1840
 Lys Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp
 1845 1850 1855
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 1860 1865 1870
 Arg Lys Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp
 1875 1880 1885
 Asp Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys
 1890 1895 1900
 Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile Leu
 1905 1910 1915 1920
 Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr
 1925 1930 1935
 His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro Lys
 1940 1945 1950
 Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro Leu Glu Asn Asp
 1955 1960 1965
 Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met Leu Leu Asp Asn Ile
 1970 1975 1980
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 1985 1990 1995 2000
 Lys Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu Arg Gly Glu Ala Arg
 2005 2010 2015
 Lys Thr Phe Val Asp Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu
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 Cys Phe Asp Gly Val Lys Asn Asn Gln Ile Leu Glu Glu Asn Val Glu
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 2065 2070 2075 2080
 Trp Leu Asp Ala Arg Ile Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe
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 Glu Met Gly Arg Leu Pro Thr Phe Met Thr Gln Lys Ala Arg Asp Ala
 2115 2120 2125
 Leu Asp Asn Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala
 2130 2135 2140
 Tyr Asn His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu Leu
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217

Leu Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu Phe Leu
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 2225 2230 2235 2240
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 2275 2280 2285
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 2290 2295 2300
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 2340 2345 2350
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 Thr Gln Val Leu Met Met Arg Thr Thr Trp Ala Leu Cys Glu Ala Leu
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 Thr Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp Glu Gly Asn Pro Gly
 2450 2455 2460
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 2465 2470 2475 2480
 Gly Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe Ser Ile Met Lys Asn
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 Thr Thr Asn Thr Arg Arg Gly Thr Gly Asn Ile Gly Glu Thr Leu Gly
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 Glu Lys Trp Lys Ser Arg Leu Asn Ala Leu Gly Lys Ser Glu Phe Gln
 2515 2520 2525
 Ile Tyr Lys Lys Ser Gly Ile Gln Glu Val Asp Arg Thr Leu Ala Lys
 2530 2535 2540
 Glu Gly Ile Lys Arg Gly Glu Thr Asp His His Ala Val Ser Arg Gly
 2545 2550 2555 2560
 Ser Ala Lys Leu Arg Trp Phe Val Glu Arg Asn Met Val Thr Pro Glu
 2565 2570 2575
 Gly Lys Val Val Asp Leu Gly Cys Gly Arg Gly Gly Trp Ser Tyr Tyr
 2580 2585 2590

218

Cys Gly Gly Leu Lys Asn Val Arg Glu Val Lys Gly Leu Thr Lys Gly
 2595 2600 2605
 Gly Pro Gly His Glu Glu Pro Ile Pro Met Ser Thr Tyr Gly Trp Asn
 2610 2615 2620
 Leu Val Arg Leu Gln Ser Gly Val Asp Val Phe Phe Ile Pro Pro Glu
 2625 2630 2635 2640
 Lys Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro
 2645 2650 2655
 Thr Val Glu Ala Gly Arg Thr Leu Arg Val Leu Asn Leu Val Glu Asn
 2660 2665 2670
 Trp Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys Val Leu Asn Pro Tyr
 2675 2680 2685
 Met Pro Ser Val Ile Glu Lys Met Glu Ala Leu Gln Arg Lys Tyr Gly
 2690 2695 2700
 Gly Ala Leu Val Arg Asn Pro Leu Ser Arg Asn Ser Thr His Glu Met
 2705 2710 2715 2720
 Tyr Trp Val Ser Asn Ala Ser Gly Asn Ile Val Ser Ser Val Asn Met
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 Thr Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly Thr Arg Asn Ile Gly
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 2915 2920 2925
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 2945 2950 2955 2960
 Glu Lys Lys Leu Gly Glu Phe Gly Lys Ala Lys Gly Ser Arg Ala Ile
 2965 2970 2975
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 2980 2985 2990
 Phe Leu Asn Glu Asp His Trp Phe Ser Arg Glu Asn Ser Leu Ser Gly
 2995 3000 3005
 Val Glu Gly Glu Gly Leu His Lys Leu Gly Tyr Ile Leu Arg Asp Val
 3010 3015 3020

219

Ser Lys Lys Glu Gly Gly Ala Met Tyr Ala Asp Asp Thr Ala Gly Trp
 3025 3030 3035 3040
 Asp Thr Arg Ile Thr Leu Glu Asp Leu Lys Asn Glu Glu Met Val Thr
 3045 3050 3055
 Asn His Met Glu Gly Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys
 3060 3065 3070
 Leu Thr Tyr Gln Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg
 3075 3080 3085
 Gly Thr Val Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly
 3090 3095 3100
 Gln Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln
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 Leu Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile Gln His
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 Gly Arg Glu Arg Leu Ser Arg Met Ala Ile Ser Gly Asp Asp Cys Val
 3155 3160 3165
 Val Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala Leu Thr Ala Leu Asn
 3170 3175 3180
 Asp Met Gly Lys Ile Arg Lys Asp Ile Gln Gln Trp Glu Pro Ser Arg
 3185 3190 3195 3200
 Gly Trp Asn Asp Trp Thr Gln Val Pro Phe Cys Ser His His Phe His
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 Glu Leu Ile Met Lys Asp Gly Arg Val Leu Val Val Pro Cys Arg Asn
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 Gln Asp Glu Leu Ile Gly Arg Ala Arg Ile Ser Gln Gly Ala Gly Trp
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 3250 3255 3260
 Ser Leu Met Tyr Phe His Arg Arg Asp Leu Arg Leu Ala Ala Asn Ala
 3265 3270 3275 3280
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 3285 3290 3295
 Trp Ser Ile His Ala Lys His Glu Trp Met Thr Thr Glu Asp Met Leu
 3300 3305 3310
 Thr Val Trp Asn Arg Val Trp Ile Gln Glu Asn Pro Trp Met Glu Asp
 3315 3320 3325
 Lys Thr Pro Val Glu Ser Trp Glu Glu Ile Pro Tyr Leu Gly Lys Arg
 3330 3335 3340
 Glu Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala Thr
 3345 3350 3355 3360
 Trp Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln Val Arg Ser Leu Ile
 3365 3370 3375
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 3380 3385 3390
 Arg Glu Glu Glu Ala Gly Val Leu Trp
 3395 3400

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<211> 10699

<212> DNA

<213> Artificial Sequence

<220>

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<223> Description of Artificial Sequence:/Note =
synthetic construct

<221> CDS

<222> (95)...(10267)

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Met Asn Asn Gln Arg Lys Lys	
1 5	
acg gga aaa cgg tct atc aat atg ctg aaa cgc gtg aga aac cgt gtg	163
Thr Gly Lys Pro Ser Ile Asn Met Leu Lys Arg Val Arg Asn Arg Val	
10 15 20	
tca act gga tca cag ttg cgg aag aga ttc tca aga gga ttg ctg aac	211
Ser Thr Gly Ser Gln Leu Ala Lys Arg Phe Ser Arg Gly Leu Leu Asn	
25 30 35	
ggc caa gga cca atg aaa ttg gtt atg gca ttt ata gct ttc ctc aga	259
Gly Gln Gly Pro Met Lys Leu Val Met Ala Phe Ile Ala Phe Leu Arg	
40 45 50 55	
ttt cta gcc att cca cgg aca gca gga gtc ttg gct aga tgg ggt acc	307
Phe Leu Ala Ile Pro Pro Thr Ala Gly Val Leu Ala Arg Trp Gly Thr	
60 65 70	
ttt aag aag tcg ggg gct att aag gtc tta aaa ggc ttc aag aag gag	355
Phe Lys Lys Ser Gly Ala Ile Lys Val Leu Lys Gly Phe Lys Lys Glu	
75 80 85	
atc tca aac atg ctg agc att atc aac aaa cgg aaa aag aca tcg ctc	403
Ile Ser Asn Met Leu Ser Ile Ile Asn Lys Arg Lys Lys Thr Ser Leu	
90 95 100	
tgt ctc atg atg atg tta cca gca aca ctt gct ttc cac tta act tca	451
Cys Leu Met Met Met Leu Pro Ala Thr Leu Ala Phe His Leu Thr Ser	
105 110 115	
cga gat gga gag cgg cgc atg att gtg ggg aag aat gaa aga gga aaa	499
Arg Asp Gly Glu Pro Arg Met Ile Val Gly Lys Asn Glu Arg Gly Lys	
120 125 130 135	
tcc cta ctt ttc aag aca gcc tct gga atc aac atg tgc aca ctc ata	547
Ser Leu Leu Phe Lys Thr Ala Ser Gly Ile Asn Met Cys Thr Leu Ile	
140 145 150	
gcc atg gat ctg gga gag atg tgt gat gac acg gtc act tac aaa tgc	595
Ala Met Asp Leu Gly Glu Met Cys Asp Asp Thr Val Thr Tyr Lys Cys	
155 160 165	

221

ccc cac att acc gaa gtg gag cct gaa gac att gac tgc tgg tgc aac	643
Pro His Ile Thr Glu Val Glu Pro Glu Asp Ile Asp Cys Trp Cys Asn	
170 175 180	
ctt aca tcg aca tgg gtg act tat gga aca tgc aat caa gct gga gag	691
Leu Thr Ser Thr Trp Val Thr Tyr Gly Thr Cys Asn Gln Ala Gly Glu	
185 190 195	
cat aga cgc gat aag aga tca gtg gcg tta gct ccc cat gtt ggc atg	739
His Arg Arg Asp Lys Arg Ser Val Ala Leu Ala Pro His Val Gly Met	
200 205 210 215	
gga ctg gac aca cgc act caa acc tgg atg tcg gct gaa gga gct tgg	787
Gly Leu Asp Thr Arg Thr Gln Thr Trp Met Ser Ala Glu Gly Ala Trp	
220 225 230	
aga caa gtc gag aag gta gag aca tgg gcc ctt agg cac cca ggg ttt	835
Arg Gln Val Glu Lys Val Glu Thr Trp Ala Leu Arg His Pro Gly Phe	
235 240 245	
acc ata cta gcc cta ttt ctt gcc cat tac ata ggc act tcc ttg acc	883
Thr Ile Leu Ala Leu Phe Leu Ala His Tyr Ile Gly Thr Ser Leu Thr	
250 255 260	
cag aaa gtg gtt att ttt ata cta tta atg ctg gtt acc cca tcc atg	931
Gln Lys Val Val Ile Phe Ile Leu Leu Met Leu Val Thr Pro Ser Met	
265 270 275	
aca atg aga tgt gta gga gta gga aac aga gat ttt gtg gaa ggc cta	979
Thr Met Arg Cys Val Gly Val Gly Asn Arg Asp Phe Val Glu Gly Leu	
280 285 290 295	
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Ser Gly Ala Thr Trp Val Asp Val Val Leu Glu His Gly Gly Cys Val	
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act acc atg gct aag aac aag ccc acg ctg gac ata gag ctt cag aag	1075
Thr Thr Met Ala Lys Asn Lys Pro Thr Leu Asp Ile Glu Leu Gln Lys	
315 320 325	
acc gag gcc acc caa ctg gcg acc cta agg aag cta tgc att gag gga	1123
Thr Glu Ala Thr Gln Leu Ala Thr Leu Arg Lys Leu Cys Ile Glu Gly	
330 335 340	
aaa att acc aac ata aca acc gac tca aga tgt ccc acc caa ggg gaa	1171
Lys Ile Thr Asn Ile Thr Thr Asp Ser Arg Cys Pro Thr Gln Gly Glu	
345 350 355	
gcg att tta cct gag gag cag gac cag aac tac gtg tgt aag cat aca	1219
Ala Ile Leu Pro Glu Glu Gln Asp Gln Asn Tyr Val Cys Lys His Thr	
360 365 370 375	
tac gtg gac aga ggc tgg gga aac ggt tgt ggt ttg ttt ggc aag gga	1267
Tyr Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly Lys Gly	
380 385 390	

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aaa gtg gtg caa cat gag aac ctc aaa tac acc gtc atc atc aca gtg Lys Val Val Gln His Glu Asn Leu Lys Tyr Thr Val Ile Ile Thr Val 410 415 420	1363
cac aca gga gac caa cac cag gtg gga aat gaa acg cag gga gtc acg His Thr Gly Asp Gln His Gln Val Gly Asn Glu Thr Gln Gly Val Thr 425 430 435	1411
gct gag ata aca ccc cag gca tca acc gct gaa gcc att tta cct gaa Ala Glu Ile Thr Pro Gln Ala Ser Thr Ala Glu Ala Ile Leu Pro Glu 440 445 450 455	1459
tat gga acc ctc ggg cta gaa tgc tca cca cgg aca ggt ttg gat ttc Tyr Gly Thr Leu Gly Leu Glu Cys Ser Pro Arg Thr Gly Leu Asp Phe 460 465 470	1507
aat gaa atg atc tca ttg aca atg aag aac aaa gca tgg atg gta cat Asn Glu Met Ile Ser Leu Thr Met Lys Asn Lys Ala Trp Met Val His 475 480 485	1555
aga caa tgg ttc ttt gac tta ccc cta cca tgg aca tca gga gct aca Arg Gln Trp Phe Phe Asp Leu Pro Leu Pro Trp Thr Ser Gly Ala Thr 490 495 500	1603
gca gaa aca cca act tgg aac agg aaa gag ctt ctt gtg aca ttt aaa Ala Glu Thr Pro Thr Trp Asn Arg Lys Glu Leu Leu Val Thr Phe Lys 505 510 515	1651
aat gca cat gca aaa aag caa gaa gta gtt gtt ctt gga tca caa gag Asn Ala His Ala Lys Lys Gln Glu Val Val Val Leu Gly Ser Gln Glu 520 525 530 535	1699
gga gca atg cat aca gca ctg aca gga gct aca gag atc caa acc tca Gly Ala Met His Thr Ala Leu Thr Gly Ala Thr Glu Ile Gln Thr Ser 540 545 550	1747
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223

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gcc aat cca gtg gtg acc aag aag gag gag cct gtc aac att gag gct Ala Asn Pro Val Val Thr Lys Lys Glu Glu Pro Val Asn Ile Glu Ala 635 640 645	2035
gaa cct cct ttt gga gaa agt aac ata gta att gga att gga gac aaa Glu Pro Pro Phe Gly Glu Ser Asn Ile Val Ile Gly Ile Gly Asp Lys 650 655 660	2083
gcc ctg aaa atc aac tgg tac aag aag gga agc tgc att ggg aag atg Ala Leu Lys Ile Asn Trp Tyr Lys Lys Gly Ser Ser Ile Gly Lys Met 665 670 675	2131
ttc gag gcc act gcc aga ggt gca agg cgc atg gcc atc ttg gga gac Phe Glu Ala Thr Ala Arg Gly Ala Arg Arg Met Ala Ile Leu Gly Asp 680 685 690 695	2179
aca gcc tgg gac ttt gga tca gtg ggt ggt gtt ttg aat tca tta ggg Thr Ala Trp Asp Phe Gly Ser Val Gly Gly Val Leu Asn Ser Leu Gly 700 705 710	2227
aaa atg gtc cac caa ata ttt ggg agt gct tac aca gcc cta ttt ggt Lys Met Val His Gln Ile Phe Gly Ser Ala Tyr Thr Ala Leu Phe Gly 715 720 725	2275
gga gtc tcc tgg atg atg aaa att gga ata ggt gtc ctc tta acc tgg Gly Val Ser Trp Met Met Lys Ile Gly Ile Gly Val Leu Leu Thr Trp 730 735 740	2323
ata ggg ttg aac tca aaa aat act tct atg tca ttt tca tgc atc gcg Ile Gly Leu Asn Ser Lys Asn Thr Ser Met Ser Phe Ser Cys Ile Ala 745 750 755	2371
ata gga atc att aca ctc tat ctg gga gcc gtg gtg caa gct gac atg Ile Gly Ile Ile Thr Leu Tyr Leu Gly Ala Val Val Gln Ala Asp Met 760 765 770 775	2419
ggg tgt gtc ata aac tgg aaa ggc aaa gaa ctc aaa tgt gga agt gga Gly Cys Val Ile Asn Trp Lys Gly Lys Glu Leu Lys Cys Gly Ser Gly 780 785 790	2467
att ttc gtc act aat gag gtc cac acc tgg aca gag caa tac aaa ttt Ile Phe Val Thr Asn Glu Val His Thr Trp Thr Glu Gln Tyr Lys Phe 795 800 805	2515
caa gca gac tcc ccc aag aga ctg gca aca gcc att gca ggc gct tgg Gln Ala Asp Ser Pro Lys Arg Leu Ala Thr Ala Ile Ala Gly Ala Trp 810 815 820	2563

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gaa aat gga gtg tgc gga att agg tca aca acc aga atg gag aac ctc Glu Asn Gly Val Cys Gly Ile Arg Ser Thr Thr Arg Met Glu Asn Leu 825 830 835	2611
ttg tgg aag caa ata gcc aat gaa ctg aat tac ata tta tgg gaa aac Leu Trp Lys Gln Ile Ala Asn Glu Leu Asn Tyr Ile Leu Trp Glu Asn 840 845 850 855	2659
aac att aaa tta acg gta gtt gta ggc gac ata act ggg gtc tta gag Asn Ile Lys Leu Thr Val Val Val Gly Asp Ile Thr Gly Val Leu Glu 860 865 870	2707
caa ggg aaa aga aca cta aca cca caa ccc atg gag cta aaa tat tct Gln Gly Lys Arg Thr Leu Thr Pro Gln Pro Met Glu Leu Lys Tyr Ser 875 880 885	2755
tgg aaa aca tgg gga aag gca aaa ata gtg aca gct gaa aca caa aat Trp Lys Thr Trp Gly Lys Ala Lys Ile Val Thr Ala Glu Thr Gln Asn 890 895 900	2803
tcc tct ttc ata ata gat ggg cca agc aca ccg gag tgt cca agt gcc Ser Ser Phe Ile Ile Asp Gly Pro Ser Thr Pro Glu Cys Pro Ser Ala 905 910 915	2851
tca aga gca tgg aat gtg tgg gag gtg gag gat tac ggg ttc gga gtt Ser Arg Ala Trp Asn Val Trp Glu Val Glu Asp Tyr Gly Phe Gly Val 920 925 930 935	2899
ttc aca acc aac ata tgg ctg aaa ctc cga gag gtg tac acc caa cta Phe Thr Thr Asn Ile Trp Leu Lys Leu Arg Glu Val Tyr Thr Gln Leu 940 945 950	2947
tgt gac cat agg cta atg tcg gca gcc gtc aag gat gag agg gct gta Cys Asp His Arg Leu Met Ser Ala Ala Val Lys Asp Glu Arg Ala Val 955 960 965	2995
cat gcc gac atg ggc tat tgg ata gaa agc caa aag aat ggg agt tgg His Ala Asp Met Gly Tyr Trp Ile Glu Ser Gln Lys Asn Gly Ser Trp 970 975 980	3043
aag cta gaa aaa gca tcc ttc ata gag gtg aaa acc tgc aca tgg cca Lys Leu Glu Lys Ala Ser Phe Ile Glu Val Lys Thr Cys Thr Trp Pro 985 990 995	3091
aaa tca cac act ctc tgg agc aat ggt gtg cta gag agt gac atg att Lys Ser His Thr Leu Trp Ser Asn Gly Val Leu Glu Ser Asp Met Ile 1000 1005 1010 1015	3139
atc cca aag agt cta gct ggt ccc att tcg caa cac aac cac agg ccc Ile Pro Lys Ser Leu Ala Gly Pro Ile Ser Gln His Asn His Arg Pro 1020 1025 1030	3187

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ggg tac cac acc caa acg gca gga ccc tgg cac tta gga aaa ttg gag Gly Tyr His Thr Gln Thr Ala Gly Pro Trp His Leu Gly Lys Leu Glu 1035 1040 1045	3235
ctg gac ttc aac tat tgt gaa gga aca aca gtt gtc atc tca gaa aac Leu Asp Phe Asn Tyr Cys Glu Gly Thr Thr Val Val Ile Ser Glu Asn 1050 1055 1060	3283
tgt ggg aca aga ggc cca tca ttg aga aca aca acg gtg tca ggg aag Cys Gly Thr Arg Gly Pro Ser Leu Arg Thr Thr Thr Val Ser Gly Lys 1065 1070 1075	3331
ttg ata cac gaa tgg tgc tgc cgc tgc tgc aca ctt cct ccc cta cga Leu Ile His Glu Trp Cys Cys Arg Ser Cys Thr Leu Pro Pro Leu Arg 1080 1085 1090 1095	3379
tac atg gga gaa gac ggc tgc tgg tat ggc atg gaa atc aga ccc att Tyr Met Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile Arg Pro Ile 1100 1105 1110	3427
aat gag aaa gaa gag aat atg gta aag tct cta gcc tca gca ggg agt Asn Glu Lys Glu Glu Asn Met Val Lys Ser Leu Ala Ser Ala Gly Ser 1115 1120 1125	3475
gga aag gtg gac aac ttc aca atg ggt gtc ttg tgt ttg gca atc ctc Gly Lys Val Asp Asn Phe Thr Met Gly Val Leu Cys Leu Ala Ile Leu 1130 1135 1140	3523
ttt gaa gag gtg atg aga gga aaa ttt ggg aaa aca cac atg att gca Phe Glu Glu Val Met Arg Gly Lys Phe Gly Lys Lys His Met Ile Ala 1145 1150 1155	3571
ggg gtt ctc ttc acg ttt gtg ctc ctc ctc tca ggg caa ata aca tgg Gly Val Leu Phe Thr Phe Val Leu Leu Leu Ser Gly Gln Ile Thr Trp 1160 1165 1170 1175	3619
aga gac atg gcg cac aca ctc ata atg att ggg tcc aac gcc tct gac Arg Asp Met Ala His Thr Leu Ile Met Ile Gly Ser Asn Ala Ser Asp 1180 1185 1190	3667
aga atg ggg atg ggc gtc act tac cta gct cta att gca aca ttt aaa Arg Met Gly Met Gly Val Thr Tyr Leu Ala Leu Ile Ala Thr Phe Lys 1195 1200 1205	3715
att cag cca ttc ctg gct ttg gga ttc ttc ctg agg aaa ctg aca tct Ile Gln Pro Phe Leu Ala Leu Gly Phe Phe Leu Arg Lys Leu Thr Ser 1210 1215 1220	3763
aga gaa aat tta ttg ctg gga gtt ggg ttg gcc atg gca gca acg tta Arg Glu Asn Leu Leu Leu Gly Val Gly Leu Ala Met Ala Ala Thr Leu 1225 1230 1235	3811
cga ctg cca gag gac att gaa cag atg gcg aat gga att gct ttg ggg Arg Leu Pro Glu Asp Ile Glu Gln Met Ala Asn Gly Ile Ala Leu Gly 1240 1245 1250 1255	3859

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ctc atg gct ctt aaa ctg ata aca caa ttt gaa aca tac caa cta tgg Leu Met Ala Leu Lys Leu Ile Thr Gln Phe Glu Thr Tyr Gln Leu Trp 1260 1265 1270	3907
acg gca tta gtt tcc cta acg tgt tca aat aca att ttc acg ttg act Thr Ala Leu Val Ser Leu Thr Cys Ser Asn Thr Ile Phe Thr Leu Thr 1275 1280 1285	3955
gtt gcc tgg aga aca gcc act ctg att tta gcc gga att tcg ctt ttg Val Ala Trp Arg Thr Ala Thr Leu Ile Leu Ala Gly Ile Ser Leu Leu 1290 1295 1300	4003
cca gtg tgc cag tct tcg agc atg agg aaa aca gat tgg ctc cca atg Pro Val Cys Gln Ser Ser Ser Met Arg Lys Thr Asp Trp Leu Pro Met 1305 1310 1315	4051
act gtg gca gct atg gga gct caa ccc cta cca ctt ttt att ttc agt Thr Val Ala Ala Met Gly Ala Gln Pro Leu Pro Leu Phe Ile Phe Ser 1320 1325 1330 1335	4099
ctg aaa gat aca ctc aaa agg aga agc tgg cca ctg aat gag ggg gtg Leu Lys Asp Thr Leu Lys Arg Arg Ser Trp Pro Leu Asn Glu Gly Val 1340 1345 1350	4147
atg gca gtt gga ctt gtg agc att cta gct agt tct ctc ctt agg aat Met Ala Val Gly Leu Val Ser Ile Leu Ala Ser Ser Leu Leu Arg Asn 1355 1360 1365	4195
gat gtg cct atg gct gga cca tta gtg gct ggg ggc ttg ctg ata gcg Asp Val Pro Met Ala Gly Pro Leu Val Ala Gly Gly Leu Leu Ile Ala 1370 1375 1380	4243
tgc tac gtc ata act ggc acg tca gca gac ctc act gta gaa aaa gca Cys Tyr Val Ile Thr Gly Thr Ser Ala Asp Leu Thr Val Glu Lys Ala 1385 1390 1395	4291
gca gat gta aca tgg gag gaa gag gcc gag caa aca gga gtg tcc cac Ala Asp Val Thr Trp Glu Glu Glu Ala Glu Gln Thr Gly Val Ser His 1400 1405 1410 1415	4339
aat tta atg gtc aca gtt gat gat gat gga aca atg aga ata aaa gat Asn Leu Met Val Thr Val Asp Asp Asp Gly Thr Met Arg Ile Lys Asp 1420 1425 1430	4387
gac gag act gag aac atc tta aca gtg ctt tta aaa aca gca cta cta Asp Glu Thr Glu Asn Ile Leu Thr Val Leu Leu Lys Thr Ala Leu Leu 1435 1440 1445	4435
ata gta tca ggc atc ttt cca tac tcc ata ccc gca aca ctg ttg gtc Ile Val Ser Gly Ile Phe Pro Tyr Ser Ile Pro Ala Thr Leu Leu Val 1450 1455 1460	4483

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tgg cat act tgg caa aag caa acc caa aga tcc ggc gtc cta tgg gac Trp His Thr Trp Gln Lys Gln Thr Gln Arg Ser Gly Val Leu Trp Asp 1465 1470 1475	4531
gta ccc agc ccc cca gag aca cag aaa gcg gaa ctg gaa gaa ggg gtc Val Pro Ser Pro Pro Glu Thr Gln Lys Ala Glu Leu Glu Glu Gly Val 1480 1485 1490 1495	4579
tat agg atc aaa cag caa gga att ttt ggg aaa acc caa gtg ggg gtt Tyr Arg Ile Lys Gln Gln Gly Ile Phe Gly Lys Thr Gln Val Gly Val 1500 1505 1510	4627
gga gta cag aaa gaa gga gtt ttc cac acc atg tgg cat gtc aca aga Gly Val Gln Lys Glu Gly Val Phe His Thr Met Trp His Val Thr Arg 1515 1520 1525	4675
ggg gca gtg ttg aca cac aat ggg aaa aga ctg gaa cca aac tgg gct Gly Ala Val Leu Thr His Asn Gly Lys Arg Leu Glu Pro Asn Trp Ala 1530 1535 1540	4723
agc gtg aaa aaa gat ctg att tca tac gga gga gga tgg aga ttg agt Ser Val Lys Lys Asp Leu Ile Ser Tyr Gly Gly Trp Arg Leu Ser 1545 1550 1555	4771
gca caa tgg caa aag ggg gag gag gtg cag gtt att gcc gta gag cct Ala Gln Trp Gln Lys Gly Glu Glu Val Gln Val Ile Ala Val Glu Pro 1560 1565 1570 1575	4819
ggg aag aac cca aag aac ttt caa acc atg cca ggc att ttt cag aca Gly Lys Asn Pro Lys Asn Phe Gln Thr Met Pro Gly Ile Phe Gln Thr 1580 1585 1590	4867
aca aca ggg gaa ata gga gca att gca ctg gat ttc aag cct gga act Thr Thr Gly Glu Ile Gly Ala Ile Ala Leu Asp Phe Lys Pro Gly Thr 1595 1600 1605	4915
tca gga tct ccc atc ata aac aga gag gga aag gta gtg gga ctg tat Ser Gly Ser Pro Ile Ile Asn Arg Glu Gly Lys Val Val Gly Leu Tyr 1610 1615 1620	4963
ggc aat gga gtg gtt aca aag aat gga ggc tat gtc agt gga ata gcg Gly Asn Gly Val Val Thr Lys Asn Gly Gly Tyr Val Ser Gly Ile Ala 1625 1630 1635	5011
caa aca aat gca gaa cca gat gga ccg aca cca gag ttg gaa gaa gag Gln Thr Asn Ala Glu Pro Asp Gly Pro Thr Pro Glu Leu Glu Glu Glu 1640 1645 1650 1655	5059
atg ttc aaa aag cga aat cta acc ata atg gat ctc cat cct ggg tca Met Phe Lys Lys Arg Asn Leu Thr Ile Met Asp Leu His Pro Gly Ser 1660 1665 1670	5107
gga aag acg cgg aaa tat ctt cca gct att gtt aga gag gca atc aag Gly Lys Thr Arg Lys Tyr Leu Pro Ala Ile Val Arg Glu Ala Ile Lys 1675 1680 1685	5155

aga cgc tta agg act cta att ttg gca cca aca agg gta gtt gca gct Arg Arg Leu Arg Thr Leu Ile Leu Ala Pro Thr Arg Val Val Ala Ala 1690 1695 1700	5203
gag atg gaa gaa gca ttg aaa ggg ctc cca ata agg tat caa aca act Glu Met Glu Glu Ala Leu Lys Gly Leu Pro Ile Arg Tyr Gln Thr Thr 1705 1710 1715	5251
gca aca aaa tct gaa cac aca gga aga gag att gtt gat cta atg tgt Ala Thr Lys Ser Glu His Thr Gly Arg Glu Ile Val Asp Leu Met Cys 1720 1725 1730 1735	5299
cac gca acg ttc aca atg cgc ttg ctg tca cca gtc agg gtt cca aac His Ala Thr Phe Thr Met Arg Leu Leu Ser Pro Val Arg Val Pro Asn 1740 1745 1750	5347
tac aac ttg ata ata atg gat gag gcc cat ttc aca gac cca gcc agt Tyr Asn Leu Ile Ile Met Asp Glu Ala His Phe Thr Asp Pro Ala Ser 1755 1760 1765	5395
ata gcg gct aga ggg tac ata tca act cgt gta gga atg gga gag gca Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Gly Met Gly Glu Ala 1770 1775 1780	5443
gcc gca att ttc atg aca gca aca ccc cct gga aca gct gat gcc ttt Ala Ala Ile Phe Met Thr Ala Thr Pro Pro Gly Thr Ala Asp Ala Phe 1785 1790 1795	5491
cct cag agc aac gct cca att caa gat gaa gag aga gac ata ccg gaa Pro Gln Ser Asn Ala Pro Ile Gln Asp Glu Glu Arg Asp Ile Pro Glu 1800 1805 1810 1815	5539
cgc tca tgg aat tca ggc aat gaa tgg att act gac ttt gtt ggg aag Arg Ser Trp Asn Ser Gly Asn Glu Trp Ile Thr Asp Phe Val Gly Lys 1820 1825 1830	5587
aca gtg tgg ttt gtc cct agc atc aaa gcc gga aat gac ata gca aac Thr Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile Ala Asn 1835 1840 1845	5635
tgc ttg cgg aaa aat gga aaa aag gtt att caa ctc agc agg aag acc Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg Lys Thr 1850 1855 1860	5683
ttt gac aca gaa tat caa aag acc aaa ctg aat gat tgg gac ttt gtg Phe Asp Thr Glu Tyr Gln Lys Thr Lys Leu Asn Asp Trp Asp Phe Val 1865 1870 1875	5731
gtg aca aca gac att tca gaa atg gga gcc aat ttc aaa gca gat aga Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys Ala Asp Arg 1880 1885 1890 1895	5779

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gtg atc gac cca aga aga tgt ctc aag ccg gtg att ttg aca gat gga Val Ile Asp Pro Arg Arg Cys Leu Lys Pro Val Ile Leu Thr Asp Gly 1900 1905 1910	5827
ccc gag cgg gtg atc ctg gct gga cca atg cca gtc acc gta gcg agc Pro Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr Val Ala Ser 1915 1920 1925	5875
gct gcg caa agg aga ggg aga gtt ggc agg aac cca caa aaa gaa aat Ala Ala Gln Arg Arg Gly Arg Val Gly Arg Asn Pro Gln Lys Glu Asn 1930 1935 1940	5923
gac cag tac ata ttc atg ggc cag cct ctc aac aat gat gaa gac cat Asp Gln Tyr Ile Phe Met Gly Gln Pro Leu Asn Asn Asp Glu Asp His 1945 1950 1955	5971
gct cac tgg aca gaa gca aaa atg ctg ctg gac aac atc aac aca cca Ala His Trp Thr Glu Ala Lys Met Leu Leu Asp Asn Ile Asn Thr Pro 1960 1965 1970 1975	6019
gaa ggg att ata cca gct ctc ttt gaa cca gaa agg gag aag tca gcc Glu Gly Ile Ile Pro Ala Leu Phe Glu Pro Glu Arg Glu Lys Ser Ala 1980 1985 1990	6067
gcc ata gac ggc gaa tac cgc ctg aag ggt gag tcc agg aag act ttc Ala Ile Asp Gly Glu Tyr Arg Leu Lys Gly Glu Ser Arg Lys Thr Phe 1995 2000 2005	6115
gtg gaa ctc atg agg agg ggt gac ctc cca gtt tgg cta gcc cat aaa Val Glu Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ala His Lys 2010 2015 2020	6163
gta gca tca gaa ggg atc aaa tat aca gat aga aaa tgg tgc ttt gat Val Ala Ser Glu Gly Ile Lys Tyr Thr Asp Arg Lys Trp Cys Phe Asp 2025 2030 2035	6211
gga gaa cgt aat aat caa att tta gag gag aat atg gat gtg gaa atc Gly Glu Arg Asn Asn Gln Ile Leu Glu Glu Asn Met Asp Val Glu Ile 2040 2045 2050 2055	6259
tgg aca aag gaa gga gaa aag aaa aaa ctg aga cct agg tgg ctt gat Trp Thr Lys Glu Gly Glu Lys Lys Lys Leu Arg Pro Arg Trp Leu Asp 2060 2065 2070	6307
gcc cgc act tat tca gat cct tta gca ctc aaa gaa ttc aag gat ttt Ala Arg Thr Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys Asp Phe 2075 2080 2085	6355
gca gct ggc aga aag tca atc gcc ctt gat ctt gtg aca gaa ata gga Ala Ala Gly Arg Lys Ser Ile Ala Leu Asp Leu Val Thr Glu Ile Gly 2090 2095 2100	6403
aga gtg cct tca cac tta gcc cac aga acg aga aac gcc ctg gat aat Arg Val Pro Ser His Leu Ala His Arg Thr Arg Asn Ala Leu Asp Asn 2105 2110 2115	6451

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ttg gtg atg ctg cac acg tca gaa cat ggc ggt agg gcc tac agg cat Leu Val Met Leu His Thr Ser Glu His Gly Gly Arg Ala Tyr Arg His 2120 2125 2130 2135	6499
gca gtg gag gaa cta cca gaa acg atg gaa aca ctc tta ctc ctg gga Ala Val Glu Glu Leu Pro Glu Thr Met Glu Thr Leu Leu Leu Leu Gly 2140 2145 2150	6547
ctg atg atc ttg tta aca ggt gga gca atg cjc ttc ttg ata tca ggt Leu Met Ile Leu Leu Thr Gly Gly Ala Met Leu Phe Leu Ile Ser Gly 2155 2160 2165	6595
aaa ggg att gga aag act tca ata gga ctc att tgt gta att gct tcc Lys Gly Ile Gly Lys Thr Ser Ile Gly Leu Ile Cys Val Ile Ala Ser 2170 2175 2180	6643
agc ggc atg tta tgg atg gct gat gtc cca ctc caa tgg atc gca tcg Ser Gly Met Leu Trp Met Ala Asp Val Pro Leu Gln Trp Ile Ala Ser 2185 2190 2195	6691
gct ata gtc ctg gag ttt ttt atg atg gtg ttg ctc ata cca gaa cca Ala Ile Val Leu Glu Phe Phe Met Met Val Leu Leu Ile Pro Glu Pro 2200 2205 2210 2215	6739
gaa aag cag aga act ccc caa gac aac caa ctc gca tat gtc gtg ata Glu Lys Gln Arg Thr Pro Gln Asp Asn Gln Leu Ala Tyr Val Val Ile 2220 2225 2230	6787
ggc ata ctt aca ttg gct gca ata gta gcg gcc aat gaa atg gga ctg Gly Ile Leu Thr Leu Ala Ala Ile Val Ala Ala Asn Glu Met Gly Leu 2235 2240 2245	6835
ttg gaa act aca aag aga gat tta gga atg tct aaa gaa cca ggt gtt Leu Glu Thr Thr Lys Arg Asp Leu Gly Met Ser Lys Glu Pro Gly Val 2250 2255 2260	6883
gtt tct cca acc agc tat ttg gat gtg gac ttg cac cca gca tca gcc Val Ser Pro Thr Ser Tyr Leu Asp Val Asp Leu His Pro Ala Ser Ala 2265 2270 2275	6931
tgg aca ttg tac gcc gtg gcc aca aca gta ata aca cca atg ttg aga Trp Thr Leu Tyr Ala Val Ala Thr Thr Val Ile Thr Pro Met Leu Arg 2280 2285 2290 2295	6979
cac acc ata gag aat tcc aca gca aat gtg tct ctg gca gcc ata gct His Thr Ile Glu Asn Ser Thr Ala Asn Val Ser Leu Ala Ala Ile Ala 2300 2305 2310	7027
aac cag gca gtg gtc ctg atg ggt tta gac aaa gga tgg cog ata tcg Asn Gln Ala Val Val Leu Met Gly Leu Asp Lys Gly Trp Pro Ile Ser 2315 2320 2325	7075

231

aaa atg gac ttg ggc gta cca cta ttg gca ctg ggt tgc tat tca caa Lys Met Asp Leu Gly Val Pro Leu Leu Ala Leu Gly Cys Tyr Ser Gln 2330 2335 2340	7123
gtg aac cca cta act ctt gca gcg gca gta ctt ttg cta gtc aca cat Val Asn Pro Leu Thr Leu Ala Ala Val Leu Leu Val Thr His 2345 2350 2355	7171
tat gca att ata ggt cca gga ttg cag gca aaa gcc acc cgt gaa gct Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg Glu Ala 2360 2365 2370 2375	7219
cag aaa agg aca gct gct gga ata atg aag aat cca acg gtg gat gga Gln Lys Arg Thr Ala Ala Gly Ile Met Lys Asn Pro Thr Val Asp Gly 2380 2385 2390	7267
ata atg aca ata gac cta gat cct gta ata tat gat tca aaa ttt gaa Ile Met Thr Ile Asp Leu Asp Pro Val Ile Tyr Asp Ser Lys Phe Glu 2395 2400 2405	7315
aag caa cta gga cag gtc atg ctc ctg gtt ctg tgt gca gtc caa ctt Lys Gln Leu Gly Gln Val Met Leu Leu Val Leu Cys Ala Val Gln Leu 2410 2415 2420	7363
tta ttg atg aga aca tca tgg gcc ttg tgt gaa gtt cta acc cta gcc Leu Leu Met Arg Thr Ser Trp Ala Leu Cys Glu Val Leu Thr Leu Ala 2425 2430 2435	7411
aca gga cca ata aca aca ctc tgg gaa gga tca cct ggg aag ttc tgg Thr Gly Pro Ile Thr Thr Leu Trp Glu Gly Ser Pro Gly Lys Phe Trp 2440 2445 2450 2455	7459
aac acc acg ata gct gtt tcc atg gcg aac atc ttt aga ggg agc tat Asn Thr Thr Ile Ala Val Ser Met Ala Asn Ile Phe Arg Gly Ser Tyr 2460 2465 2470	7507
tta gca gga gct ggg ctt gct ttt tct atc atg aaa tca gtt gga aca Leu Ala Gly Ala Gly Leu Ala Phe Ser Ile Met Lys Ser Val Gly Thr 2475 2480 2485	7555
gga aag aga gga aca ggg tca caa ggt gaa acc tta gga gaa aag tgg Gly Lys Arg Gly Thr Gly Ser Gln Gly Glu Thr Leu Gly Glu Lys Trp 2490 2495 2500	7603
aaa aag aaa tta aat cag tta tcc cgg aaa gag ttt gac ctt tac aag Lys Lys Lys Leu Asn Gln Leu Ser Arg Lys Glu Phe Asp Leu Tyr Lys 2505 2510 2515	7651
aaa tcc gga atc acc gaa gtg gat aga aca gaa gcc aaa gaa ggg tta Lys Ser Gly Ile Thr Glu Val Asp Arg Thr Glu Ala Lys Glu Gly Leu 2520 2525 2530 2535	7699
aaa aga gga gaa ata aca cac cat gcc gtg tcc aga gcc agc gca aaa Lys Arg Gly Glu Ile Thr His His Ala Val Ser Arg Gly Ser Ala Lys 2540 2545 2550	7747

232

ctt caa tgg ttc gtg gag aga aac atg gtc att cct gaa gga aga gtc Leu Gln Trp Phe Val Glu Arg Asn Met Val Ile Pro Glu Gly Arg Val 2555 2560 2565	7795
ata gac cta ggc tgt gga aga gga ggc tgg tca tat tac tgt gca gga Ile Asp Leu Gly Cys Gly Arg Gly Gly Trp Ser Tyr Tyr Cys Ala Gly 2570 2575 2580	7843
ctg aaa aaa gtt aca gaa gtg cga gga tac aca aaa ggc ggc cca gga Leu Lys Lys Val Thr Glu Val Arg Gly Tyr Thr Lys Gly Gly Pro Gly 2585 2590 2595	7891
cac gaa gaa cca gta cct atg tct aca tac gga tgg aac ata gtc aag His Glu Glu Pro Val Pro Met Ser Thr Tyr Gly Trp Asn Ile Val Lys 2600 2605 2610 2615	7939
tta atg agt gga aag gat gtt ttt tat ctg cca cct gaa aag tgt gat Leu Met Ser Gly Lys Asp Val Phe Tyr Leu Pro Pro Glu Lys Cys Asp 2620 2625 2630	7987
acc cta ttg tgt gac att gga gaa tct tca cca agc cca aca gtg gaa Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Ser Pro Thr Val Glu 2635 2640 2645	8035
gaa agc aga acc ata aga gtt ttg aag atg gtt gaa cca tgg cta aag Glu Ser Arg Thr Ile Arg Val Leu Lys Met Val Glu Pro Trp Leu Lys 2650 2655 2660	8083
aac aac cag ttt tgc att aaa gta ttg aac cca tac atg cca act gtg Asn Asn Gln Phe Cys Ile Lys Val Leu Asn Pro Tyr Met Pro Thr Val 2665 2670 2675	8131
att gag cac tta gaa aga cta caa agg aaa cat gga gga atg ctt gtg Ile Glu His Leu Glu Arg Leu Gln Arg Lys His Gly Gly Met Leu Val 2680 2685 2690 2695	8179
aga aat cca ctc tca cga aac tcc acg cac gaa atg tat tgg ata tcc Arg Asn Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr Trp Ile Ser 2700 2705 2710	8227
aat ggt aca ggc aat atc gtc tct tca gtc aac atg gta tcc aga ttg Asn Gly Thr Gly Asn Ile Val Ser Ser Val Asn Met Val Ser Arg Leu 2715 2720 2725	8275
cta ctg aac aga ttc aca atg aca cac agg aga ccc acc ata gag aaa Leu Leu Asn Arg Phe Thr Met Thr His Arg Arg Pro Thr Ile Glu Lys 2730 2735 2740	8323
gat gtg gat cta gga gca gga acc cga cat gtc aat gcg gaa cca gaa Asp Val Asp Leu Gly Ala Gly Thr Arg His Val Asn Ala Glu Pro Glu 2745 2750 2755	8371

233

aca ccc aac atg gat gtc att ggg gaa aga ata aaa agg atc aaa gag Thr Pro Asn Met Asp Val Ile Gly Glu Arg Ile Lys Arg Ile Lys Glu 2760 2765 2770 2775	8419
gag cat agt tca aca tgg cac tat gat gat gaa aat cct tac aaa acg Glu His Ser Ser Thr Trp His Tyr Asp Asp Glu Asn Pro Tyr Lys Thr 2780 2785 2790	8467
tgg gct tac cat gga tcc tat gaa gta aaa gcc aca ggc tca gcc tcc Trp Ala Tyr His Gly Ser Tyr Glu Val Lys Ala Thr Gly Ser Ala Ser 2795 2800 2805	8515
tcc atg ata aat gga gtc gtg aaa ctc ctc aca aaa cca tgg gat gtg Ser Met Ile Asn Gly Val Val Lys Leu Leu Thr Lys Pro Trp Asp Val 2810 2815 2820	8563
gtg ccc atg gtg aca cag atg gca atg aca gat aca act cca ttc ggc Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr Pro Phe Gly 2825 2830 2835	8611
cag caa aga gtt ttt aaa gag aaa gtg gac acc agg aca cct agg ccc Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr Pro Arg Pro 2840 2845 2850 2855	8659
atg cca gga aca aga aag gtt atg gag atc aca gcg gag tgg ctt tgg Met Pro Gly Thr Arg Lys Val Met Glu Ile Thr Ala Glu Trp Leu Trp 2860 2865 2870	8707
agg acc ctg gga agg aac aaa aga ccc aga tta tgc aca agg gag gaa Arg Thr Leu Gly Arg Asn Lys Arg Pro Arg Leu Cys Thr Arg Glu Glu 2875 2880 2885	8755
ttc aca aag aag gtc aga acc aac gca gct atg ggc gct gtc ttc aca Phe Thr Lys Lys Val Arg Thr Asn Ala Ala Met Gly Ala Val Phe Thr 2890 2895 2900	8803
gaa gag aac caa tgg gac agt gcg aga gct gct gtt gag gac gaa gaa Glu Glu Asn Gln Trp Asp Ser Ala Arg Ala Ala Val Glu Asp Glu Glu 2905 2910 2915	8851
ttt tgg aaa ctt gtg gac aga gaa cgt gaa ctc cac aaa ctg ggc aag Phe Trp Lys Leu Val Asp Arg Glu Arg Glu Leu His Lys Leu Gly Lys 2920 2925 2930 2935	8899
tgt gga agc tgc gtt tac aac atg atg ggc aag aga gag aaa aaa ctt Cys Gly Ser Cys Val Tyr Asn Met Met Gly Lys Arg Glu Lys Lys Leu 2940 2945 2950	8947
gga gag ttt ggt aaa gca aaa ggc agt agg gct ata tgg tac atg tgg Gly Glu Phe Gly Lys Ala Lys Gly Ser Arg Ala Ile Trp Tyr Met Trp 2955 2960 2965	8995
ttg gga gcc agg tac ctt gag ttc gag gcg ctc gga ttc ctc aat gaa Leu Gly Ala Arg Tyr Leu Glu Phe Glu Ala Leu Gly Phe Leu Asn Glu 2970 2975 2980	9043

gac cac tgg ttc tgc cgt gaa aac tct tac agt gga gta gaa gga gaa Asp His Trp Phe Ser Arg Glu Asn Ser Tyr Ser Gly Val Glu Gly Glu 2985 2990 2995	9091
gga ctg cac aag ctg gga tac atc ttg aga gat att tcc aag ata ccc Gly Leu His Lys Leu Gly Tyr Ile Leu Arg Asp Ile Ser Lys Ile Pro 3000 3005 3010 3015	9139
gga gga gcc atg tat gct gat gac aca gcc ggt tgg gac aca aga ata Gly Gly Ala Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp Thr Arg Ile 3020 3025 3030	9187
aca gaa gat gac ctg cac aat gag gaa aaa atc aca cag cag atg gac Thr Glu Asp Asp Leu His Asn Glu Glu Lys Ile Thr Gln Gln Met Asp 3035 3040 3045	9235
cct gaa cac agg cag cta gcg aac gct ata ttc aag ctc aca tac caa Pro Glu His Arg Gln Leu Ala Asn Ala Ile Phe Lys Leu Thr Tyr Gln 3050 3055 3060	9283
aac aaa gtg gtc aaa gtc caa cga cca act cca aag gcc acg gta atg Asn Lys Val Val Lys Val Gln Arg Pro Thr Pro Lys Gly Thr Val Met 3065 3070 3075	9331
gac atc ata tct agg aaa gac caa aga gcc agt gga cag gtg gga act Asp Ile Ile Ser Arg Lys Asp Gln Arg Gly Ser Gly Gln Val Gly Thr 3080 3085 3090 3095	9379
tat ggt ctg aac aca ttc acc aac atg gaa gcc cag cta atc aga caa Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu Ile Arg Gln 3100 3105 3110	9427
atg gaa gga gaa gcc gtg ttg tca aag gca gac ctc gag aac ccc cat Met Glu Gly Glu Gly Val Leu Ser Lys Ala Asp Leu Glu Asn Pro His 3115 3120 3125	9475
ccg cta gag aag aaa att aca caa tgg ttg gaa act aaa gga gtg gaa Pro Leu Glu Lys Lys Ile Thr Gln Trp Leu Glu Thr Lys Gly Val Glu 3130 3135 3140	9523
agg tta aaa aga atg gcc atc agc ggg gat gat tgc gtt gtg aaa cca Arg Leu Lys Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val Lys Pro 3145 3150 3155	9571
atc gac gac aga ttc gcc aat gcc ctg ctt gcc ctg aac gat atg gga Ile Asp Asp Arg Phe Ala Asn Ala Leu Leu Ala Leu Asn Asp Met Gly 3160 3165 3170 3175	9619
aag gtt aga aag gac ata cct caa tgg cag cca tca aag gga tgg cat Lys Val Arg Lys Asp Ile Pro Gln Trp Gln Pro Ser Lys Gly Trp His 3180 3185 3190	9667

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gat tgg caa cag gtc ccc ttc tgc tcc cac cac ttt cat gaa ttg atc Asp Trp Gln Gln Val Pro Phe Cys Ser His His Phe His Glu Leu Ile 3195 3200 3205	9715
atg aaa gat gga aga aag ttg gta gtt ccc tgc aga ccc cag gac gaa Met Lys Asp Gly Arg Lys Leu Val Val Pro Cys Arg Pro Gln Asp Glu 3210 3215 3220	9763
cta ata gga aga gcg aga atc tcc caa gga gca gga tgg agc ctt aga Leu Ile Gly Arg Ala Arg Ile Ser Gln Gly Ala Gly Trp Ser Leu Arg 3225 3230 3235	9811
gaa act gca tgt cta ggg aaa gcc tac gct caa atg tgg gct ctc atg Glu Thr Ala Cys Leu Gly Lys Ala Tyr Ala Gln Met Trp Ala Leu Met 3240 3245 3250 3255	9859
tat ttt cac aga aga gat ctt aga cta gca tcc aac gcc ata tgt tca Tyr Phe His Arg Arg Asp Leu Arg Leu Ala Ser Asn Ala Ile Cys Ser 3260 3265 3270	9907
gca gta cca gtc cac tgg gtc ccc acg agc aga acg aca tgg tct att Ala Val Pro Val His Trp Val Pro Thr Ser Arg Thr Thr Ser Ile 3275 3280 3285	9955
cat gct cac cat cag tgg atg act aca gaa gac atg ctt act gtc tgg His Ala His His Gln Trp Met Thr Thr Glu Asp Met Leu Thr Val Trp 3290 3295 3300	10003
aac agg gtg tgg ata gag gac aat cca tgg atg gaa gac aaa act cca Asn Arg Val Trp Ile Glu Asp Asn Pro Trp Met Glu Asp Lys Thr Pro 3305 3310 3315	10051
gtc aca acg tgg gaa gat gtt cca tat cta ggg aag aga gaa gac caa Val Thr Thr Trp Glu Asp Val Pro Tyr Leu Gly Lys Arg Glu Asp Gln 3320 3325 3330 3335	10099
tgg tgc gga tca ctc ata ggt ctc act tcc aga gca acc tgg gcc cag Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala Thr Trp Ala Gln 3340 3345 3350	10147
aac ata ctc aca gca atc caa cag gtg aga agc ctc ata ggc aat gaa Asn Ile Leu Thr Ala Ile Gln Gln Val Arg Ser Leu Ile Gly Asn Glu 3355 3360 3365	10195
gag ttt ctg gac tac atg cct tcg atg aag aga ttc agg aag gag gag Glu Phe Leu Asp Tyr Met Pro Ser Met Lys Arg Phe Arg Lys Glu Glu 3370 3375 3380	10243
gag tca gag gga gcc att tgg taa aagcaggagg taaactgtca ggccacatta Glu Ser Glu Gly Ala Ile Trp * 3385 3390	10297
agccacagta cggaagaagc tgtgcagcct gtgagcccg tccaaggacg ttaaaagaag aagtcaggcc caaaagccac ggtttgagca aacgtgtgtg cctgtagetc cgctgtgggg acgtaaagcc tggggaggctg caaacctgtg aagctgtacg caggtgtag cagactagtg	10357 10417 10477

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gttagaggag acccctccca tgacacaacg cagcagcggg gcccgagcac tgaggggaagc 10537
tgtacctctc tgcaaggac tagaggttag aggagacccc ccgcaaacaa aaacagcata 10597
ttgacgtgg gagagaccag agatcctgct gtctcctcag catcattcca ggcacagaac 10657
gccagaaaaa ggaatggtgc tgttgaatca acaggttcta gt 10699

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<210> 20

<211> 3390

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<400> 20

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Met Asn Asn Gln Arg Lys Lys Thr Gly Lys Pro Ser Ile Asn Met Leu
  1          5          10          15
Lys Arg Val Arg Asn Arg Val Ser Thr Gly Ser Gln Leu Ala Lys Arg
          20          25          30
Phe Ser Arg Gly Leu Leu Asn Gly Gln Gly Pro Met Lys Leu Val Met
          35          40          45
Ala Phe Ile Ala Phe Leu Arg Phe Leu Ala Ile Pro Pro Thr Ala Gly
          50          55          60
Val Leu Ala Arg Trp Gly Thr Phe Lys Lys Ser Gly Ala Ile Lys Val
          65          70          75          80
Leu Lys Gly Phe Lys Lys Glu Ile Ser Asn Met Leu Ser Ile Ile Asn
          85          90          95
Lys Arg Lys Lys Thr Ser Leu Cys Leu Met Met Met Leu Pro Ala Thr
          100          105          110
Leu Ala Phe His Leu Thr Ser Arg Asp Gly Glu Pro Arg Met Ile Val
          115          120          125
Gly Lys Asn Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ala Ser Gly
          130          135          140
Ile Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Met Cys Asp
          145          150          155          160
Asp Thr Val Thr Tyr Lys Cys Pro His Ile Thr Glu Val Glu Pro Glu
          165          170          175
Asp Ile Asp Cys Trp Cys Asn Leu Thr Ser Thr Trp Val Thr Tyr Gly
          180          185          190
Thr Cys Asn Gln Ala Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala
          195          200          205
Leu Ala Pro His Val Gly Met Gly Leu Asp Thr Arg Thr Gln Thr Trp
          210          215          220
Met Ser Ala Glu Gly Ala Trp Arg Gln Val Glu Lys Val Glu Thr Trp
          225          230          235          240
Ala Leu Arg His Pro Gly Phe Thr Ile Leu Ala Leu Phe Leu Ala His
          245          250          255
Tyr Ile Gly Thr Ser Leu Thr Gln Lys Val Val Ile Phe Ile Leu Leu
          260          265          270
Met Leu Val Thr Pro Ser Met Thr Met Arg Cys Val Gly Val Gly Asn
          275          280          285
Arg Asp Phe Val Glu Gly Leu Ser Gly Ala Thr Trp Val Asp Val Val
          290          295          300

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Leu	Glu	His	Gly	Gly	Cys	Val	Thr	Thr	Met	Ala	Lys	Asn	Lys	Pro	Thr	305	310	315	320
Leu	Asp	Ile	Glu	Leu	Gln	Lys	Thr	Glu	Ala	Thr	Gln	Leu	Ala	Thr	Leu	325	330	335	
Arg	Lys	Leu	Cys	Ile	Glu	Gly	Lys	Ile	Thr	Asn	Ile	Thr	Thr	Asp	Ser	340	345	350	
Arg	Cys	Pro	Thr	Gln	Gly	Glu	Ala	Ile	Leu	Pro	Glu	Glu	Gln	Asp	Gln	355	360	365	
Asn	Tyr	Val	Cys	Lys	His	Thr	Tyr	Val	Asp	Arg	Gly	Trp	Gly	Asn	Gly	370	375	380	
Cys	Gly	Leu	Phe	Gly	Lys	Gly	Ser	Leu	Val	Thr	Cys	Ala	Lys	Phe	Gln	385	390	395	400
Cys	Leu	Glu	Ser	Ile	Glu	Gly	Lys	Val	Val	Gln	His	Glu	Asn	Leu	Lys	405	410	415	
Tyr	Thr	Val	Ile	Ile	Thr	Val	His	Thr	Gly	Asp	Gln	His	Gln	Val	Gly	420	425	430	
Asn	Glu	Thr	Gln	Gly	Val	Thr	Ala	Glu	Ile	Thr	Pro	Gln	Ala	Ser	Thr	435	440	445	
Ala	Glu	Ala	Ile	Leu	Pro	Glu	Tyr	Gly	Thr	Leu	Gly	Leu	Glu	Cys	Ser	450	455	460	
Pro	Arg	Thr	Gly	Leu	Asp	Phe	Asn	Glu	Met	Ile	Ser	Leu	Thr	Met	Lys	465	470	475	480
Asn	Lys	Ala	Trp	Met	Val	His	Arg	Gln	Trp	Phe	Phe	Asp	Leu	Pro	Leu	485	490	495	
Pro	Trp	Thr	Ser	Gly	Ala	Thr	Ala	Glu	Thr	Pro	Thr	Trp	Asn	Arg	Lys	500	505	510	
Glu	Leu	Leu	Val	Thr	Phe	Lys	Asn	Ala	His	Ala	Lys	Lys	Gln	Glu	Val	515	520	525	
Val	Val	Leu	Gly	Ser	Gln	Glu	Gly	Ala	Met	His	Thr	Ala	Leu	Thr	Gly	530	535	540	
Ala	Thr	Glu	Ile	Gln	Thr	Ser	Gly	Gly	Thr	Ser	Ile	Phe	Ala	Gly	His	545	550	555	560
Leu	Lys	Cys	Arg	Leu	Lys	Met	Asp	Lys	Leu	Glu	Leu	Lys	Gly	Met	Ser	565	570	575	
Tyr	Ala	Met	Cys	Leu	Ser	Ser	Phe	Val	Leu	Lys	Lys	Glu	Val	Ser	Glu	580	585	590	
Thr	Gln	His	Gly	Thr	Ile	Leu	Ile	Lys	Val	Glu	Tyr	Lys	Gly	Glu	Asp	595	600	605	
Ala	Pro	Cys	Lys	Ile	Pro	Phe	Ser	Thr	Glu	Asp	Gly	Gln	Gly	Lys	Ala	610	615	620	
His	Asn	Gly	Arg	Leu	Ile	Thr	Ala	Asn	Pro	Val	Val	Thr	Lys	Lys	Glu	625	630	635	640
Glu	Pro	Val	Asn	Ile	Glu	Ala	Glu	Pro	Pro	Phe	Gly	Glu	Ser	Asn	Ile	645	650	655	
Val	Ile	Gly	Ile	Gly	Asp	Lys	Ala	Leu	Lys	Ile	Asn	Trp	Tyr	Lys	Lys	660	665	670	
Gly	Ser	Ser	Ile	Gly	Lys	Met	Phe	Glu	Ala	Thr	Ala	Arg	Gly	Ala	Arg	675	680	685	
Arg	Met	Ala	Ile	Leu	Gly	Asp	Thr	Ala	Trp	Asp	Phe	Gly	Ser	Val	Gly	690	695	700	
Gly	Val	Leu	Asn	Ser	Leu	Gly	Lys	Met	Val	His	Gln	Ile	Phe	Gly	Ser	705	710	715	720
Ala	Tyr	Thr	Ala	Leu	Phe	Gly	Gly	Val	Ser	Trp	Met	Met	Lys	Ile	Gly	725	730	735	

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Ile Gly Val Leu Leu Thr Trp Ile Gly Leu Asn Ser Lys Asn Thr Ser
 740 745 750
 Met Ser Phe Ser Cys Ile Ala Ile Gly Ile Ile Thr Leu Tyr Leu Gly
 755 760 765
 Ala Val Val Gln Ala Asp Met Gly Cys Val Ile Asn Trp Lys Gly Lys
 770 775 780
 Glu Leu Lys Cys Gly Ser Gly Ile Phe Val Thr Asn Glu Val His Thr
 785 790 795 800
 Trp Thr Glu Gln Tyr Lys Phe Gln Ala Asp Ser Pro Lys Arg Leu Ala
 805 810 815
 Thr Ala Ile Ala Gly Ala Trp Glu Asn Gly Val Cys Gly Ile Arg Ser
 820 825 830
 Thr Thr Arg Met Glu Asn Leu Leu Trp Lys Gln Ile Ala Asn Glu Leu
 835 840 845
 Asn Tyr Ile Leu Trp Glu Asn Asn Ile Lys Leu Thr Val Val Val Gly
 850 855 860
 Asp Ile Thr Gly Val Leu Glu Gln Gly Lys Arg Thr Leu Thr Pro Gln
 865 870 875 880
 Pro Met Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala Lys Ile
 885 890 895
 Val Thr Ala Glu Thr Gln Asn Ser Ser Phe Ile Ile Asp Gly Pro Ser
 900 905 910
 Thr Pro Glu Cys Pro Ser Ala Ser Arg Ala Trp Asn Val Trp Glu Val
 915 920 925
 Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu Lys Leu
 930 935 940
 Arg Glu Val Tyr Thr Gln Leu Cys Asp His Arg Leu Met Ser Ala Ala
 945 950 955 960
 Val Lys Asp Glu Arg Ala Val His Ala Asp Met Gly Tyr Trp Ile Glu
 965 970 975
 Ser Gln Lys Asn Gly Ser Trp Lys Leu Glu Lys Ala Ser Phe Ile Glu
 980 985 990
 Val Lys Thr Cys Thr Trp Pro Lys Ser His Thr Leu Trp Ser Asn Gly
 995 1000 1005
 Val Leu Glu Ser Asp Met Ile Ile Pro Lys Ser Leu Ala Gly Pro Ile
 1010 1015 1020
 Ser Gln His Asn His Arg Pro Gly Tyr His Thr Gln Thr Ala Gly Pro
 1025 1030 1035 1040
 Trp His Leu Gly Lys Leu Glu Leu Asp Phe Asn Tyr Cys Glu Gly Thr
 1045 1050 1055
 Thr Val Val Ile Ser Glu Asn Cys Gly Thr Arg Gly Pro Ser Leu Arg
 1060 1065 1070
 Thr Thr Thr Val Ser Gly Lys Leu Ile His Glu Trp Cys Cys Arg Ser
 1075 1080 1085
 Cys Thr Leu Pro Pro Leu Arg Tyr Met Gly Glu Asp Gly Cys Trp Tyr
 1090 1095 1100
 Gly Met Glu Ile Arg Pro Ile Asn Glu Lys Glu Glu Asn Met Val Lys
 1105 1110 1115 1120
 Ser Leu Ala Ser Ala Gly Ser Gly Lys Val Asp Asn Phe Thr Met Gly
 1125 1130 1135
 Val Leu Cys Leu Ala Ile Leu Phe Glu Glu Val Met Arg Gly Lys Phe
 1140 1145 1150
 Gly Lys Lys His Met Ile Ala Gly Val Leu Phe Thr Phe Val Leu Leu
 1155 1160 1165

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Leu Ser Gly Gln Ile Thr Trp Arg Asp Met Ala His Thr Leu Ile Met
 1170 1175 1180
 Ile Gly Ser Asn Ala Ser Asp Arg Met Gly Met Gly Val Thr Tyr Leu
 1185 1190 1195 1200
 Ala Leu Ile Ala Thr Phe Lys Ile Gln Pro Phe Leu Ala Leu Gly Phe
 1205 1210 1215
 Phe Leu Arg Lys Leu Thr Ser Arg Glu Asn Leu Leu Leu Gly Val Gly
 1220 1225 1230
 Leu Ala Met Ala Ala Thr Leu Arg Leu Pro Glu Asp Ile Glu Gln Met
 1235 1240 1245
 Ala Asn Gly Ile Ala Leu Gly Leu Met Ala Leu Lys Leu Ile Thr Gln
 1250 1255 1260
 Phe Glu Thr Tyr Gln Leu Trp Thr Ala Leu Val Ser Leu Thr Cys Ser
 1265 1270 1275 1280
 Asn Thr Ile Phe Thr Leu Thr Val Ala Trp Arg Thr Ala Thr Leu Ile
 1285 1290 1295
 Leu Ala Gly Ile Ser Leu Leu Pro Val Cys Gln Ser Ser Ser Met Arg
 1300 1305 1310
 Lys Thr Asp Trp Leu Pro Met Thr Val Ala Ala Met Gly Ala Gln Pro
 1315 1320 1325
 Leu Pro Leu Phe Ile Phe Ser Leu Lys Asp Thr Leu Lys Arg Arg Ser
 1330 1335 1340
 Trp Pro Leu Asn Glu Gly Val Met Ala Val Gly Leu Val Ser Ile Leu
 1345 1350 1355 1360
 Ala Ser Ser Leu Leu Arg Asn Asp Val Pro Met Ala Gly Pro Leu Val
 1365 1370 1375
 Ala Gly Gly Leu Leu Ile Ala Cys Tyr Val Ile Thr Gly Thr Ser Ala
 1380 1385 1390
 Asp Leu Thr Val Glu Lys Ala Ala Asp Val Thr Trp Glu Glu Glu Ala
 1395 1400 1405
 Glu Gln Thr Gly Val Ser His Asn Leu Met Val Thr Val Asp Asp Asp
 1410 1415 1420
 Gly Thr Met Arg Ile Lys Asp Asp Glu Thr Glu Asn Ile Leu Thr Val
 1425 1430 1435 1440
 Leu Leu Lys Thr Ala Leu Leu Ile Val Ser Gly Ile Phe Pro Tyr Ser
 1445 1450 1455
 Ile Pro Ala Thr Leu Leu Val Trp His Thr Trp Gln Lys Gln Thr Gln
 1460 1465 1470
 Arg Ser Gly Val Leu Trp Asp Val Pro Ser Pro Pro Glu Thr Gln Lys
 1475 1480 1485
 Ala Glu Leu Glu Glu Gly Val Tyr Arg Ile Lys Gln Gln Gly Ile Phe
 1490 1495 1500
 Gly Lys Thr Gln Val Gly Val Gly Val Gln Lys Glu Gly Val Phe His
 1505 1510 1515 1520
 Thr Met Trp His Val Thr Arg Gly Ala Val Leu Thr His Asn Gly Lys
 1525 1530 1535
 Arg Leu Glu Pro Asn Trp Ala Ser Val Lys Lys Asp Leu Ile Ser Tyr
 1540 1545 1550
 Gly Gly Gly Trp Arg Leu Ser Ala Gln Trp Gln Lys Gly Glu Glu Val
 1555 1560 1565
 Gln Val Ile Ala Val Glu Pro Gly Lys Asn Pro Lys Asn Phe Gln Thr
 1570 1575 1580
 Met Pro Gly Ile Phe Gln Thr Thr Thr Gly Glu Ile Gly Ala Ile Ala
 1585 1590 1595 1600

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Leu	Asp	Phe	Lys	Pro	Gly	Thr	Ser	Gly	Ser	Pro	Ile	Ile	Asn	Arg	Glu	
				1605					1610					1615		
Gly	Lys	Val	Val	Gly	Leu	Tyr	Gly	Asn	Gly	Val	Val	Thr	Lys	Asn	Gly	
				1620					1625					1630		
Gly	Tyr	Val	Ser	Gly	Ile	Ala	Gln	Thr	Asn	Ala	Glu	Pro	Asp	Gly	Pro	
				1635					1640					1645		
Thr	Pro	Glu	Leu	Glu	Glu	Glu	Met	Phe	Lys	Lys	Arg	Asn	Leu	Thr	Ile	
				1650					1655					1660		
Met	Asp	Leu	His	Pro	Gly	Ser	Gly	Lys	Thr	Arg	Lys	Tyr	Leu	Pro	Ala	
				1665										1680		
Ile	Val	Arg	Glu	Ala	Ile	Lys	Arg	Arg	Leu	Arg	Thr	Leu	Ile	Leu	Ala	
				1685										1695		
Pro	Thr	Arg	Val	Val	Ala	Ala	Glu	Met	Glu	Glu	Ala	Leu	Lys	Gly	Leu	
				1700					1705					1710		
Pro	Ile	Arg	Tyr	Gln	Thr	Thr	Ala	Thr	Lys	Ser	Glu	His	Thr	Gly	Arg	
				1715					1720					1725		
Glu	Ile	Val	Asp	Leu	Met	Cys	His	Ala	Thr	Phe	Thr	Met	Arg	Leu	Leu	
				1730					1735					1740		
Ser	Pro	Val	Arg	Val	Pro	Asn	Tyr	Asn	Leu	Ile	Ile	Met	Asp	Glu	Ala	
				1745										1760		
His	Phe	Thr	Asp	Pro	Ala	Ser	Ile	Ala	Ala	Arg	Gly	Tyr	Ile	Ser	Thr	
				1765										1775		
Arg	Val	Gly	Met	Gly	Glu	Ala	Ala	Ala	Ile	Phe	Met	Thr	Ala	Thr	Pro	
				1780										1790		
Pro	Gly	Thr	Ala	Asp	Ala	Phe	Pro	Gln	Ser	Asn	Ala	Pro	Ile	Gln	Asp	
				1795										1805		
Glu	Glu	Arg	Asp	Ile	Pro	Glu	Arg	Ser	Trp	Asn	Ser	Gly	Asn	Glu	Trp	
				1810										1820		
Ile	Thr	Asp	Phe	Val	Gly	Lys	Thr	Val	Trp	Phe	Val	Pro	Ser	Ile	Lys	
				1825										1840		
Ala	Gly	Asn	Asp	Ile	Ala	Asn	Cys	Leu	Arg	Lys	Asn	Gly	Lys	Lys	Val	
				1845										1855		
Ile	Gln	Leu	Ser	Arg	Lys	Thr	Phe	Asp	Thr	Glu	Tyr	Gln	Lys	Thr	Lys	
				1860										1870		
Leu	Asn	Asp	Trp	Asp	Phe	Val	Val	Thr	Thr	Asp	Ile	Ser	Glu	Met	Gly	
				1875										1885		
Ala	Asn	Phe	Lys	Ala	Asp	Arg	Val	Ile	Asp	Pro	Arg	Arg	Cys	Leu	Lys	
				1890										1900		
Pro	Val	Ile	Leu	Thr	Asp	Gly	Pro	Glu	Arg	Val	Ile	Leu	Ala	Gly	Pro	
				1905										1920		
Met	Pro	Val	Thr	Val	Ala	Ser	Ala	Ala	Gln	Arg	Arg	Gly	Arg	Val	Gly	
				1925										1935		
Arg	Asn	Pro	Gln	Lys	Glu	Asn	Asp	Gln	Tyr							

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Asp Arg Lys Trp Cys Phe Asp Gly Glu Arg Asn Asn Gln Ile Leu Glu
 2035 2040 2045
 Glu Asn Met Asp Val Glu Ile Trp Thr Lys Glu Gly Glu Lys Lys Lys
 2050 2055 2060
 Leu Arg Pro Arg Trp Leu Asp Ala Arg Thr Tyr Ser Asp Pro Leu Ala
 2065 2070 2075 2080
 Leu Lys Glu Phe Lys Asp Phe Ala Ala Gly Arg Lys Ser Ile Ala Leu
 2085 2090 2095
 Asp Leu Val Thr Glu Ile Gly Arg Val Pro Ser His Leu Ala His Arg
 2100 2105 2110
 Thr Arg Asn Ala Leu Asp Asn Leu Val Met Leu His Thr Ser Glu His
 2115 2120 2125
 Gly Gly Arg Ala Tyr Arg His Ala Val Glu Glu Leu Pro Glu Thr Met
 2130 2135 2140
 Glu Thr Leu Leu Leu Leu Gly Leu Met Ile Leu Leu Thr Gly Gly Ala
 2145 2150 2155 2160
 Met Leu Phe Leu Ile Ser Gly Lys Gly Ile Gly Lys Thr Ser Ile Gly
 2165 2170 2175
 Leu Ile Cys Val Ile Ala Ser Ser Gly Met Leu Trp Met Ala Asp Val
 2180 2185 2190
 Pro Leu Gln Trp Ile Ala Ser Ala Ile Val Leu Glu Phe Phe Met Met
 2195 2200 2205
 Val Leu Leu Ile Pro Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn
 2210 2215 2220
 Gln Leu Ala Tyr Val Val Ile Gly Ile Leu Thr Leu Ala Ala Ile Val
 2225 2230 2235 2240
 Ala Ala Asn Glu Met Gly Leu Leu Glu Thr Thr Lys Arg Asp Leu Gly
 2245 2250 2255
 Met Ser Lys Glu Pro Gly Val Val Ser Pro Thr Ser Tyr Leu Asp Val
 2260 2265 2270
 Asp Leu His Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr
 2275 2280 2285
 Val Ile Thr Pro Met Leu Arg His Thr Ile Glu Asn Ser Thr Ala Asn
 2290 2295 2300
 Val Ser Leu Ala Ala Ile Ala Asn Gln Ala Val Val Leu Met Gly Leu
 2305 2310 2315 2320
 Asp Lys Gly Trp Pro Ile Ser Lys Met Asp Leu Gly Val Pro Leu Leu
 2325 2330 2335
 Ala Leu Gly Cys Tyr Ser Gln Val Asn Pro Leu Thr Leu Ala Ala Ala
 2340 2345 2350
 Val Leu Leu Leu Val Thr His Tyr Ala Ile Ile Gly Pro Gly Leu Gln
 2355 2360 2365
 Ala Lys Ala Thr Arg Glu Ala Gln Lys Arg Thr Ala Ala Gly Ile Met
 2370 2375 2380
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 2385 2390 2395 2400
 Ile Tyr Asp Ser Lys Phe Glu Lys Gln Leu Gly Gln Val Met Leu Leu
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 Val Leu Cys Ala Val Gln Leu Leu Leu Met Arg Thr Ser Trp Ala Leu
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 Cys Glu Val Leu Thr Leu Ala Thr Gly Pro Ile Thr Thr Leu Trp Glu
 2435 2440 2445
 Gly Ser Pro Gly Lys Phe Trp Asn Thr Thr Ile Ala Val Ser Met Ala
 2450 2455 2460

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Asn	Ile	Phe	Arg	Gly	Ser	Tyr	Leu	Ala	Gly	Ala	Gly	Leu	Ala	Phe	Ser	2465	2470	2475	2480
Ile	Met	Lys	Ser	Val	Gly	Thr	Gly	Lys	Arg	Gly	Thr	Gly	Ser	Gln	Gly				
				2485				2490						2495					
Glu	Thr	Leu	Gly	Glu	Lys	Trp	Lys	Lys	Lys	Leu	Asn	Gln	Leu	Ser	Arg				
			2500					2505				2510							
Lys	Glu	Phe	Asp	Leu	Tyr	Lys	Lys	Ser	Gly	Ile	Thr	Glu	Val	Asp	Arg				
		2515					2520					2525							
Thr	Glu	Ala	Lys	Glu	Gly	Leu	Lys	Arg	Gly	Glu	Ile	Thr	His	His	Ala				
		2530				2535					2540								
Val	Ser	Arg	Gly	Ser	Ala	Lys	Leu	Gln	Trp	Phe	Val	Glu	Arg	Asn	Met				
2545				2550						2555				2560					
Val	Ile	Pro	Glu	Gly	Arg	Val	Ile	Asp	Leu	Gly	Cys	Gly	Arg	Gly	Gly				
			2565					2570						2575					
Trp	Ser	Tyr	Tyr	Cys	Ala	Gly	Leu	Lys	Lys	Val	Thr	Glu	Val	Arg	Gly				
			2580					2585					2590						
Tyr	Thr	Lys	Gly	Gly	Pro	Gly	His	Glu	Glu	Pro	Val	Pro	Met	Ser	Thr				
		2595				2600					2605								
Tyr	Gly	Trp	Asn	Ile	Val	Lys	Leu	Met	Ser	Gly	Lys	Asp	Val	Phe	Tyr				
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Leu	Pro	Pro	Glu	Lys	Cys	Asp	Thr	Leu	Leu	Cys	Asp	Ile	Gly	Glu	Ser				
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Ser	Pro	Ser	Pro	Thr	Val	Glu	Glu	Ser	Arg	Thr	Ile	Arg	Val	Leu	Lys				
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Met	Val	Glu	Pro	Trp	Leu	Lys	Asn	Asn	Gln	Phe	Cys	Ile	Lys	Val	Leu				
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Asn	Pro	Tyr	Met	Pro	Thr	Val	Ile	Glu	His	Leu	Glu	Arg	Leu	Gln	Arg				
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Lys	His	Gly	Gly	Met	Leu	Val	Arg	Asn	Pro	Leu	Ser	Arg	Asn	Ser	Thr				
2690				2695						2700									
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Val	Asn	Met	Val	Ser	Arg	Leu	Leu	Leu	Asn	Arg	Phe	Thr	Met	Thr	His				
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Arg	Arg	Pro	Thr	Ile	Glu	Lys	Asp	Val	Asp	Leu	Gly	Ala	Gly	Thr	Arg				
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His	Val	Asn	Ala	Glu	Pro	Glu													

243

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 Asp Asp Cys Val Val Lys Pro Ile Asp Asp Arg Phe Ala Asn Ala Leu
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 Gln Pro Ser Lys Gly Trp His Asp Trp Gln Gln Val Pro Phe Cys Ser
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 His His Phe His Glu Leu Ile Met Lys Asp Gly Arg Lys Leu Val Val
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 Pro Cys Arg Pro Gln Asp Glu Leu Ile Gly Arg Ala Arg Ile Ser Gln
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 3265 3270 3275 3280
 Ser Arg Thr Thr Trp Ser Ile His Ala His His Gln Trp Met Thr Thr
 3285 3290 3295
 Glu Asp Met Leu Thr Val Trp Asn Arg Val Trp Ile Glu Asp Asn Pro
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 Trp Met Glu Asp Lys Thr Pro Val Thr Thr Trp Glu Asp Val Pro Tyr
 3315 3320 3325

244

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  3345                3350                3355                3360
Arg Ser Leu Ile Gly Asn Glu Glu Phe Leu Asp Tyr Met Pro Ser Met
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Lys Arg Phe Arg Lys Glu Glu Glu Ser Glu Gly Ala Ile Trp
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<223> Description of Artificial Sequence:/Note =
synthetic construct

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                               Met Asn Asn Gln Arg Lys Lys
                               1                5

acg gga aaa ccg tct atc aat atg ctg aaa cgc gtg aga aac cgt gtg      163
Thr Gly Lys Pro Ser Ile Asn Met Leu Lys Arg Val Arg Asn Arg Val
      10                15                20

tca act gga tca cag ttg gcg aag aga ttc tca aga gga ttg ctg aac      211
Ser Thr Gly Ser Gln Leu Ala Lys Arg Phe Ser Arg Gly Leu Leu Asn
      25                30                35

ggc caa gga cca atg aaa ttg gtt atg gca ttt ata gct ttc ctc aga      259
Gly Gln Gly Pro Met Lys Leu Val Met Ala Phe Ile Ala Phe Leu Arg
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ttt cta gcc att cca ccg aca gca gga gtc ttg gct aga tgg ggt acc      307
Phe Leu Ala Ile Pro Pro Thr Ala Gly Val Leu Ala Arg Trp Gly Thr
      60                65                70

ttt aag aag tcg ggg gct att aag gtc tta aaa ggc ttc aag aag gag      355
Phe Lys Lys Ser Gly Ala Ile Lys Val Leu Lys Gly Phe Lys Lys Glu
      75                80                85

atc tca aac atg ctg agc att atc aac aaa cgg aaa aag aca tcg ctc      403
Ile Ser Asn Met Leu Ser Ile Ile Asn Lys Arg Lys Lys Thr Ser Leu
      90                95                100

tgt ctc atg atg atg tta cca gca aca ctt gct ttc cac tta act tca      451
Cys Leu Met Met Met Leu Pro Ala Thr Leu Ala Phe His Leu Thr Ser
      105                110                115

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245

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120 125 130 135	
tcc cta ctt ttc aag aca gcc tct gga atc aac atg tgc aca ctc ata	547
Ser Leu Leu Phe Lys Thr Ala Ser Gly Ile Asn Met Cys Thr Leu Ile	
140 145 150	
gct atg gat ctg gga gag atg tgt gat gac acg gtc act tac aaa tgc	595
Ala Met Asp Leu Gly Glu Met Cys Asp Asp Thr Val Thr Tyr Lys Cys	
155 160 165	
ccc cac att acc gaa gtg gag cct gaa gac att gac tgc tgg tgc aac	643
Pro His Ile Thr Glu Val Glu Pro Glu Asp Ile Asp Cys Trp Cys Asn	
170 175 180	
ctt aca tcg aca tgg gtg act tat gga aca tgc aat caa gct gga gag	691
Leu Thr Ser Thr Trp Val Thr Tyr Gly Thr Cys Asn Glu Ala Gly Glu	
185 190 195	
cat aga cgc gat aag aga tca gtg gcg tta gct ccc cat gtt gcc atg	739
His Arg Arg Asp Lys Arg Ser Val Ala Leu Ala Pro His Val Gly Met	
200 205 210 215	
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Gly Leu Asp Thr Arg Thr Gln Thr Trp Met Ser Ala Glu Gly Ala Trp	
220 225 230	
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Arg Gln Val Glu Lys Val Glu Thr Trp Ala Leu Arg His Pro Gly Phe	
235 240 245	
acc ata cta gcc cta ttt ctt gcc cat tac ata gcc act tcc ttg acc	883
Thr Ile Leu Ala Leu Phe Leu Ala His Tyr Ile Gly Thr Ser Leu Thr	
250 255 260	
cag aaa gtg gtt att ttt ata cta tta atg ctg gtt acc cca tcc atg	931
Gln Lys Val Val Ile Phe Ile Leu Leu Met Leu Val Thr Pro Ser Met	
265 270 275	
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Thr Met Arg Cys Val Gly Val Gly Asn Arg Asp Phe Val Glu Gly Leu	
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Ser Gly Ala Thr Trp Val Asp Val Val Leu Glu His Gly Gly Cys Val	
300 305 310	
act acc atg gct aag aac aag ccc acg ctg gac ata gag ctt cag aag	1075
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246

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gcg att tta cct gag gag cag gac cag aac tac gtg tgt aag cat aca Ala Ile Leu Pro Glu Glu Gln Asp Gln Asn Tyr Val Cys Lys His Thr 360 365 370 375	1219
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cac aca gga gac caa cac cag gtg gga aat gaa acg cag gga gtc acg His Thr Gly Asp Gln His Gln Val Gly Asn Glu Thr Gln Gly Val Thr 425 430 435	1411
gct gag ata aca ccc cag gca tca acc gct gaa gcc att tta cct gaa Ala Glu Ile Thr Pro Gln Ala Ser Thr Ala Glu Ala Ile Leu Pro Glu 440 445 450 455	1459
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gca gaa aca cca act tgg aac agg aaa gag ctt ctt gtg aca ttt aaa Ala Glu Thr Pro Thr Trp Asn Arg Lys Glu Leu Leu Val Thr Phe Lys 505 510 515	1651
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247

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att aag gtt gag tac aaa ggg aaa gat gca ccc tgc aag att cct ttc Ile Lys Val Glu Tyr Lys Gly Lys Asp Ala Pro Cys Lys Ile Pro Phe 600 605 610 615	1939
tcc acg gag gat gga caa gga aaa gct cac aat ggc aga ctg atc aca Ser Thr Glu Asp Gly Gln Gly Lys Ala His Asn Gly Arg Leu Ile Thr 620 625 630	1987
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gcc ctg aaa atc aac tgg tac aag aag gga agc tcg att ggg aag atg Ala Leu Lys Ile Asn Trp Tyr Lys Lys Gly Ser Ser Ile Gly Lys Met 665 670 675	2131
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248

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249

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250

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1355 1360 1365	
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Cys Tyr Val Ile Thr Gly Thr Ser Ala Asp Leu Thr Val Glu Lys Ala	
1385 1390 1395	
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1400 1405 1410 1415	

251

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tgg cat act tgg caa aag caa acc caa aga tcc ggc gtc cta tgg gac Trp His Thr Trp Gln Lys Gln Thr Gln Arg Ser Gly Val Leu Trp Asp 1465 1470 1475	4531
gta ccc agc ccc cca gag aca cag aaa gcg gaa ctg gaa gaa ggg gtc Val Pro Ser Pro Pro Glu Thr Gln Lys Ala Glu Leu Glu Gly Val 1480 1485 1490 1495	4579
tat agg atc aaa cag caa gga att ttt ggg aaa acc caa gtg ggg gtt Tyr Arg Ile Lys Gln Gln Gly Ile Phe Gly Lys Thr Gln Val Gly Val 1500 1505 1510	4627
gga gta cag aaa gaa gga gtt ttc cac acc atg tgg cat gtc aca aga Gly Val Gln Lys Glu Gly Val Phe His Thr Met Trp His Val Thr Arg 1515 1520 1525	4675
ggg gca gtg ttg aca cac aat ggg aaa aga ctg gaa cca aac tgg gct Gly Ala Val Leu Thr His Asn Gly Lys Arg Leu Glu Pro Asn Trp Ala 1530 1535 1540	4723
agc gtg aaa aaa gat ctg att tca tac gga gga gga tgg aga ttg agt Ser Val Lys Lys Asp Leu Ile Ser Tyr Gly Gly Gly Trp Arg Leu Ser 1545 1550 1555	4771
gca caa tgg aaa aag ggg gag gag gtg cag gtt att gcc gta gag cct Ala Gln Trp Lys Lys Gly Glu Glu Val Gln Val Ile Ala Val Glu Pro 1560 1565 1570 1575	4819
ggg aag aac cca aag aac ttt caa acc atg cca ggc att ttt cag aca Gly Lys Asn Pro Lys Asn Phe Gln Thr Met Pro Gly Ile Phe Gln Thr 1580 1585 1590	4867
aca aca ggg gaa ata gga gca att gca ctg gat ttc aag cct gga act Thr Thr Gly Glu Ile Gly Ala Ile Ala Leu Asp Phe Lys Pro Gly Thr 1595 1600 1605	4915
tca gga tct ccc atc ata aac aga gag gga aag gta gtg gga ctg tat Ser Gly Ser Pro Ile Ile Asn Arg Glu Gly Lys Val Val Gly Leu Tyr 1610 1615 1620	4963

252

ggc aat gga gtg gtt aca aag aat gga ggc tat gtc agt gga ata gcg Gly Asn Gly Val Val Thr Lys Asn Gly Gly Tyr Val Ser Gly Ile Ala 1625 1630 1635	5011
caa aca aat gca gaa cca gat gga ccg aca cca gag ttg gaa gaa gag Gln Thr Asn Ala Glu Pro Asp Gly Pro Thr Pro Glu Leu Glu Glu Glu 1640 1645 1650 1655	5059
atg ttc aaa aag cga aat cta acc ata atg gat ctc cat cct ggg tca Met Phe Lys Lys Arg Asn Leu Thr Ile Met Asp Leu His Pro Gly Ser 1660 1665 1670	5107
gga aag acg cgg aaa tat ctt cca gct att gtt aga gag gca atc aag Gly Lys Thr Arg Lys Tyr Leu Pro Ala Ile Val Arg Glu Ala Ile Lys 1675 1680 1685	5155
aga cgc tta agg act cta att ttg gca cca aca agg gta gtt gca gct Arg Arg Leu Arg Thr Leu Ile Leu Ala Pro Thr Arg Val Val Ala Ala 1690 1695 1700	5203
gag atg gaa gaa gca ttg aaa ggg ctc cca ata agg tat caa aca act Glu Met Glu Glu Ala Leu Lys Gly Leu Pro Ile Arg Tyr Gln Thr Thr 1705 1710 1715	5251
gca aca aaa tct gaa cac aca gga aga gag att gtt gat cta atg tgt Ala Thr Lys Ser Glu His Thr Gly Arg Glu Ile Val Asp Leu Met Cys 1720 1725 1730 1735	5299
cac gca acg ttc aca atg cgc ttg ctg tca cca gtc agg gtt cca aac His Ala Thr Phe Thr Met Arg Leu Leu Ser Pro Val Arg Val Pro Asn 1740 1745 1750	5347
tac aac ttg ata ata atg gat gag gcc cat ttc aca gac cca gcc agt Tyr Asn Leu Ile Ile Met Asp Glu Ala His Phe Thr Asp Pro Ala Ser 1755 1760 1765	5395
ata gcg gct aga ggg tac ata tca act cgt gta gga atg gga gag gca Ile Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Gly Met Gly Glu Ala 1770 1775 1780	5443
gcc gca att ttc atg aca gca aca ccc cct gga aca gct gat gcc ttt Ala Ala Ile Phe Met Thr Ala Thr Pro Pro Gly Thr Ala Asp Ala Phe 1785 1790 1795	5491
cct cag agc aac gct cca att caa gat gaa gag aga gac ata ccg gaa Pro Gln Ser Asn Ala Pro Ile Gln Asp Glu Glu Arg Asp Ile Pro Glu 1800 1805 1810 1815	5539
cgc tca tgg aat tca ggc aat gaa tgg att act gac ttt gtt ggg aag Arg Ser Trp Asn Ser Gly Asn Glu Trp Ile Thr Asp Phe Val Gly Lys 1820 1825 1830	5587
aca gtg tgg ttt gtc cct agc atc aaa gcc gga aat gac ata gca aac Thr Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile Ala Asn 1835 1840 1845	5635

253

tgc ttg cgg aaa aat gga aaa aag gtt att caa ctc agc agg aag acc Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg Lys Thr 1850 1855 1860	5683
ttt gac aca gaa tat caa aag acc aaa ctg aat gat tgg gac ttt gtg Phe Asp Thr Glu Tyr Gln Lys Thr Lys Leu Asn Asp Trp Asp Phe Val 1865 1870 1875	5731
gtg aca aca gac att tca gaa atg gga gcc aat ttc aaa gca gat aga Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys Ala Asp Arg 1880 1885 1890 1895	5779
gtg atc gac cca aga aga tgt ctc aag ccg gtg att ttg aca gat gga Val Ile Asp Pro Arg Arg Cys Leu Lys Pro Val Ile Leu Thr Asp Gly 1900 1905 1910	5827
ccc gag cgg gtg atc ctg gct gga cca atg cca gtc acc gta gcg agc Pro Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr Val Ala Ser 1915 1920 1925	5875
gct gcg caa agg aga ggg aga gtt ggc agg aac cca caa aaa gaa aat Ala Ala Gln Arg Arg Gly Arg Val Gly Arg Asn Pro Gln Lys Glu Asn 1930 1935 1940	5923
gac cag tac ata ttc atg ggc cag cct ctc aac aat gat gaa gac cat Asp Gln Tyr Ile Phe Met Gly Gln Pro Leu Asn Asn Asp Glu Asp His 1945 1950 1955	5971
gct cac tgg aca gaa gca aaa atg ctg ctg gac aac atc aac aca cca Ala His Trp Thr Glu Ala Lys Met Leu Leu Asp Asn Ile Asn Thr Pro 1960 1965 1970 1975	6019
gaa ggg att ata cca gct ctc ttt gaa cca gaa agg gag aag tca gcc Glu Gly Ile Ile Pro Ala Leu Phe Glu Pro Glu Arg Glu Lys Ser Ala 1980 1985 1990	6067
gcc ata gac ggc gaa tac cgc ctg aag ggt gag tcc agg aag act ttc Ala Ile Asp Gly Glu Tyr Arg Leu Lys Gly Glu Ser Arg Lys Thr Phe 1995 2000 2005	6115
gtg gaa ctc atg agg agg ggt gac ctc cca gtt tgg cta gcc cat aaa Val Glu Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ala His Lys 2010 2015 2020	6163
gta gca tca gaa ggg atc aaa tat aca gat aga aaa tgg tgc ttt gat Val Ala Ser Glu Gly Ile Lys Tyr Thr Asp Arg Lys Trp Cys Phe Asp 2025 2030 2035	6211
gga gaa cgt aat aat caa att tta gag gag aat atg gat gtg gaa atc Gly Glu Arg Asn Asn Gln Ile Leu Glu Glu Asn Met Asp Val Glu Ile 2040 2045 2050 2055	6259

254

tgg aca aag gaa gga gaa aag aaa aaa	ctg aga cct agg tgg ctt gat	6307
Trp Thr Lys Glu Gly Glu Lys Lys Lys	Leu Arg Pro Arg Trp Leu Asp	
2060	2065 2070	
gcc cgc act tat tca gat cct tta gca ctc aaa gaa ttc aag gat ttt	6355	
Ala Arg Thr Tyr Ser Asp Pro Leu Ala Leu Lys Glu Phe Lys Asp Phe		
2075	2080 2085	
gca gct ggc aga aag tca atc gcc ctt gat ctt gtg aca gaa ata gga	6403	
Ala Ala Gly Arg Lys Ser Ile Ala Leu Asp Leu Val Thr Glu Ile Gly		
2090	2095 2100	
aga gtg cct tca cac tta gcc cac aga acg aga aac gcc ctg gat aat	6451	
Arg Val Pro Ser His Leu Ala His Arg Thr Arg Asn Ala Leu Asp Asn		
2105	2110 2115	
ttg gtg atg ctg cac acg tca gaa cat ggc ggt agg gcc tac agg cat	6499	
Leu Val Met Leu His Thr Ser Glu His Gly Gly Arg Ala Tyr Arg His		
2120	2125 2130 2135	
gca gtg gag gaa cta cca gaa acg atg gaa aca ctc tta ctc ctg gga	6547	
Ala Val Glu Glu Leu Pro Glu Thr Met Glu Thr Leu Leu Leu Gly		
2140	2145 2150	
ctg atg atc ttg tta aca ggt gga gca atg ctc ttc ttg ata tca ggt	6595	
Leu Met Ile Leu Leu Thr Gly Gly Ala Met Leu Phe Leu Ile Ser Gly		
2155	2160 2165	
aaa ggg att gga aag act tca ata gga ctc att tgt gta att gct tcc	6643	
Lys Gly Ile Gly Lys Thr Ser Ile Gly Leu Ile Cys Val Ile Ala Ser		
2170	2175 2180	
agc ggc atg tta tgg atg gct gat gtc cca ctc caa tgg atc gca tcg	6691	
Ser Gly Met Leu Trp Met Ala Asp Val Pro Leu Gln Trp Ile Ala Ser		
2185	2190 2195	
gct ata gtc ctg gag ttt ttt atg atg gtg ttg ctc ata cca gaa cca	6739	
Ala Ile Val Leu Glu Phe Phe Met Met Val Leu Leu Ile Pro Glu Pro		
2200	2205 2210 2215	
gaa aag cag aga act ccc caa gac aac caa ctc gca tat gtc gtg ata	6787	
Glu Lys Gln Arg Thr Pro Gln Asp Asn Gln Leu Ala Tyr Val Val Ile		
2220	2225 2230	
ggc ata ctt aca ttg gct gca ata gta gcg gcc aat gaa atg gga ctg	6835	
Gly Ile Leu Thr Leu Ala Ala Ile Val Ala Ala Asn Glu Met Gly Leu		
2235	2240 2245	
ttg gaa act aca aag aga gat tta gga atg tct aaa gaa cca ggt gtt	6883	
Leu Glu Thr Thr Lys Arg Asp Leu Gly Met Ser Lys Glu Pro Gly Val		
2250	2255 2260	
gtt tct cca acc agc tat ttg gat gtg gac ttg cac cca gca tca gcc	6931	
Val Ser Pro Thr Ser Tyr Leu Asp Val Asp Leu His Pro Ala Ser Ala		
2265	2270 2275	

255

tcg Trp	aca Thr	ttg Leu	tac Tyr	gcc Ala	gtg Val	gcc Ala	aca Thr	aca Thr	gta Val	ata Ile	aca Thr	cca Pro	atg Met	ttg Leu	aga Arg	6979
2280 2285 2290 2295																
cac His	acc Thr	ata Ile	gag Glu	aat Asn	tcc Ser	aca Thr	gca Ala	aat Asn	gtg Val	tct Ser	ctg Leu	gca Ala	gcc Ala	ata Ile	gct Ala	7027
2300 2305 2310																
aac Asn	cag Gln	gca Ala	gtg Val	gtc Val	ctg Leu	atg Met	ggg Gly	tta Leu	gac Asp	aaa Lys	gga Gly	tgg Trp	ccg Pro	ata Ile	tcg Ser	7075
2315 2320 2325																
aaa Lys	atg Met	gac Asp	ttg Leu	ggc Gly	gta Val	cca Pro	cta Leu	ttg Leu	gca Ala	ctg Leu	ggg Gly	tgc Cys	tat Tyr	tca Ser	caa Gln	7123
2330 2335 2340																
gtg Val	aac Asn	cca Pro	cta Leu	act Thr	ctt Leu	gca Ala	gog Ala	gca Ala	gta Val	ctt Leu	ttg Leu	cta Leu	gtc Val	aca Thr	cat His	7171
2345 2350 2355																
tat Tyr	gca Ala	att Ile	ata Ile	ggg Gly	cca Pro	gga Gly	ttg Leu	cag Gln	gca Ala	aaa Lys	gcc Ala	acc Thr	ogt Arg	gaa Glu	got Ala	7219
2360 2365 2370 2375																
cag Gln	aaa Lys	agg Arg	aca Thr	gct Ala	gct Ala	gga Gly	ata Ile	atg Met	aag Lys	aat Asn	cca Pro	acg Thr	gtg Val	gat Asp	gga Gly	7267
2380 2385 2390																
ata Ile	atg Met	aca Thr	ata Ile	gac Asp	cta Leu	gat Asp	cct Pro	gta Val	ata Ile	tat Tyr	gat Asp	tca Ser	aaa Lys	ttt Phe	gaa Glu	7315
2395 2400 2405																
aag Lys	caa Gln	cta Leu	gga Gly	cag Gln	gtc Val	atg Met	ctc Leu	ctg Leu	gtt Val	ctg Leu	tgt Cys	gca Ala	gtc Val	caa Gln	ctt Leu	7363
2410 2415 2420																
tta Leu	ttg Leu	atg Met	aga Arg	aca Thr	tca Ser	tgg Trp	gcc Ala	ttg Leu	tgt Cys	gaa Glu	gtt Val	cta Leu	acc Thr	cta Leu	gcc Ala	7411
2425 2430 2435																
aca Thr	gga Gly	cca Pro	ata Ile	aca Thr	aca Thr	ctc Leu	tgg Trp	gaa Glu	gga Gly	tca Ser	cct Pro	ggg Gly	aag Lys	ttc Phe	tgg Trp	7459
2440 2445 2450 2455																
aac Asn	acc Thr	acg Thr	ata Ile	gct Ala	gtt Val	tcc Ser	atg Met	gcg Ala	aac Asn	atc Ile	ttt Phe	aga Arg	ggg Gly	agc Ser	tat Tyr	7507
2460 2465 2470																
tta Leu	gca Ala	gga Gly	gct Ala	ggg Gly	ctt Leu	gct Ala	ttt Phe	tct Ser	atc Ile	atg Met	aaa Lys	tca Ser	gtt Val	gga Gly	aca Thr	7555
2475 2480 2485																

256

gga aag aga gga aca ggg tca caa ggt gaa acc tta gga gaa aag tgg Gly Lys Arg Gly Thr Gly Ser Gln Gly Glu Thr Leu Gly Glu Lys Trp 2490 2495 2500	7603
aaa aag aaa tta aat cag tta tcc cgg aaa gag ttt gac ctt tac aag Lys Lys Lys Leu Asn Gln Leu Ser Arg Lys Glu Phe Asp Leu Tyr Lys 2505 2510 2515	7651
aaa tcc gga atc acc gaa gtg gat aga aca gaa gcc aaa gaa ggg tta Lys Ser Gly Ile Thr Glu Val Asp Arg Thr Glu Ala Lys Glu Gly Leu 2520 2525 2530 2535	7699
aaa aga gga gaa ata aca cac cat gcc gtg tcc aga ggc agc gca aaa Lys Arg Gly Glu Ile Thr His His Ala Val Ser Arg Gly Ser Ala Lys 2540 2545 2550	7747
ctt caa tgg ttc gtg gag aga aac atg gtc att cct gaa gga aga gtc Leu Gln Trp Phe Val Glu Arg Asn Met Val Ile Pro Glu Gly Arg Val 2555 2560 2565	7795
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ctg aaa aaa gtt aca gaa gtg cga gga tac aca aaa ggc ggc cca gga Leu Lys Lys Val Thr Glu Val Arg Gly Tyr Thr Lys Gly Gly Pro Gly 2585 2590 2595	7891
cac gaa gaa cca gta cct atg tct aca tac gga tgg aac ata gtc aag His Glu Glu Pro Val Pro Met Ser Thr Tyr Gly Trp Asn Ile Val Lys 2600 2605 2610 2615	7939
tta atg agt gga aag gat gtt ttt tat ctg cca cct gaa aag tgt gat Leu Met Ser Gly Lys Asp Val Phe Tyr Leu Pro Pro Glu Lys Cys Asp 2620 2625 2630	7987
acc cta ttg tgt gac att gga gaa tct tca cca agc cca aca gtg gaa Thr Leu Leu Cys Asp Ile Gly Glu Ser Pro Ser Pro Thr Val Glu 2635 2640 2645	8035
gaa agc aga acc ata aga gtt ttg aag atg gtt gaa cca tgg cta aag Glu Ser Arg Thr Ile Arg Val Leu Lys Met Val Glu Pro Trp Leu Lys 2650 2655 2660	8083
aac aac cag ttt tgc att aaa gta ttg aac cca tac atg cca act gtg Asn Asn Gln Phe Cys Ile Lys Val Leu Asn Pro Tyr Met Pro Thr Val 2665 2670 2675	8131
att gag cac tta gaa aga cta caa agg aaa cat gga gga atg ctt gtg Ile Glu His Leu Glu Arg Leu Gln Arg Lys His Gly Gly Met Leu Val 2680 2685 2690 2695	8179
aga aat cca ctc tca cga aac tcc acg cac gaa atg tat tgg ata tcc Arg Asn Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr Trp Ile Ser 2700 2705 2710	8227

257

aat ggt aca ggc aat atc gtc tct tca gtc aac atg gta tcc aga ttg	8275
Asn Gly Thr Gly Asn Ile Val Ser Ser Val Asn Met Val Ser Arg Leu	
2715 2720 2725	
cta ctg aac aga ttc aca atg aca cac agg aga ccc acc ata gag aaa	8323
Leu Leu Asn Arg Phe Thr Met Thr His Arg Arg Pro Thr Ile Glu Lys	
2730 2735 2740	
gat gtg gat cta gga gca gga acc cga cat gtc aat gcg gaa cca gaa	8371
Asp Val Asp Leu Gly Ala Gly Thr Arg His Val Asn Ala Glu Pro Glu	
2745 2750 2755	
aca ccc aac atg gat gtc att ggg gaa aga ata aaa agg atc aaa gag	8419
Thr Pro Asn Met Asp Val Ile Gly Glu Arg Ile Lys Arg Ile Lys Glu	
2760 2765 2770 2775	
gag cat agt tca aca tgg cac tat gat gat gaa aat cct tac aaa acg	8467
Glu His Ser Ser Thr Trp His Tyr Asp Asp Glu Asn Pro Tyr Lys Thr	
2780 2785 2790	
tgg gct tac cat gga tcc tat gaa gta aaa gcc aca ggc tca gcc tcc	8515
Trp Ala Tyr His Gly Ser Tyr Glu Val Lys Ala Thr Gly Ser Ala Ser	
2795 2800 2805	
tcc atg ata aat gga gtc gtg aaa ctc ctc aca aaa cca tgg gat gtg	8563
Ser Met Ile Asn Gly Val Val Lys Leu Leu Thr Lys Pro Trp Asp Val	
2810 2815 2820	
gtg ccc atg gtg aca cag atg gca atg aca gat aca act cca ttc ggc	8611
Val Pro Met Val Thr Gln Met Ala Met Thr Asp Thr Thr Pro Phe Gly	
2825 2830 2835	
cag caa aga gtt ttt aaa gag aaa gtg gac acc agg aca cct agg ccc	8659
Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr Pro Arg Pro	
2840 2845 2850 2855	
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Met Pro Gly Thr Arg Lys Val Met Glu Ile Thr Ala Glu Trp Leu Trp	
2860 2865 2870	
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Arg Thr Leu Gly Arg Asn Lys Arg Pro Arg Leu Cys Thr Arg Glu Glu	
2875 2880 2885	
ttc aca aag aag gtc aga acc aac gca gct atg ggc gct gtc ttc aca	8803
Phe Thr Lys Lys Val Arg Thr Asn Ala Ala Met Gly Ala Val Phe Thr	
2890 2895 2900	
gaa gag aac caa tgg gac agt gcg aga gct gct gtt gag gac gaa gaa	8851
Glu Glu Asn Gln Trp Asp Ser Ala Arg Ala Ala Val Glu Asp Glu Glu	
2905 2910 2915	

258

ttt tgg aaa ctt gtg gac aga gaa cgt gaa ctc cac aaa ctg ggc aag Phe Trp Lys Leu Val Asp Arg Glu Arg Glu Leu His Lys Leu Gly Lys 2920 2925 2930 2935	8899
tgt gga agc tgc gtt tac aac atg atg ggc aag aga gag aaa aaa ctt Cys Gly Ser Cys Val Tyr Asn Met Met Gly Lys Arg Glu Lys Lys Leu 2940 2945 2950	8947
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gga ctg cac aag ctg gga tac atc ttg aga gat att tcc aag ata ccc Gly Leu His Lys Leu Gly Tyr Ile Leu Arg Asp Ile Ser Lys Ile Pro 3000 3005 3010 3015	9139
gga gga gcc atg tat gct gat gac aca gcc ggt tgg gac aca aga ata Gly Gly Ala Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp Thr Arg Ile 3020 3025 3030	9187
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cct gaa cac agg cag cta gcg aac gct ata ttc aag ctc aca tac caa Pro Glu His Arg Gln Leu Ala Asn Ala Ile Phe Lys Leu Thr Tyr Gln 3050 3055 3060	9283
aac aaa gtg gtc aaa gtc caa cga cca act cca aag ggc acg gta atg Asn Lys Val Val Lys Val Gln Arg Pro Thr Pro Lys Gly Thr Val Met 3065 3070 3075	9331
gac atc ata tct agg aaa gac caa aga ggc agt gga cag gtg gga act Asp Ile Ile Ser Arg Lys Asp Gln Arg Gly Ser Gly Gln Val Gly Thr 3080 3085 3090 3095	9379
tat ggt ctg aac aca ttc acc aac atg gaa gcc cag cta atc aga caa Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu Ile Arg Gln 3100 3105 3110	9427
atg gaa gga gaa ggc gtg ttg tca aag gca gac ctc gag aac ccc cat Met Glu Gly Glu Gly Val Leu Ser Lys Ala Asp Leu Glu Asn Pro His 3115 3120 3125	9475
ccg cta gag aag aaa att aca caa tgg ttg gaa act aaa gga gtg gaa Pro Leu Glu Lys Lys Ile Thr Gln Trp Leu Glu Thr Lys Gly Val Glu 3130 3135 3140	9523

259

agg tta aaa aga atg gcc atc agc ggg gat gat tgc gtt gtg aaa cca Arg Leu Lys Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val Lys Pro 3145 3150 3155	9571
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aag gtt aga aag gac ata cct caa tgg cag cca tca aag gga tgg cat Lys Val Arg Lys Asp Ile Pro Gln Trp Gln Pro Ser Lys Gly Trp His 3180 3185 3190	9667
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cta ata gga aga gcg aga atc tcc caa gga gca gga tgg agc ctt aga Leu Ile Gly Arg Ala Arg Ile Ser Gln Gly Ala Gly Trp Ser Leu Arg 3225 3230 3235	9811
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gca gta cca gtc cac tgg gtc ccc acg agc aga acg aca tgg tct att Ala Val Pro Val His Trp Val Pro Thr Ser Arg Thr Thr Trp Ser Ile 3275 3280 3285	9955
cat gct cac cat cag tgg atg act aca gaa gac atg ctt act gtc tgg His Ala His His Gln Trp Met Thr Thr Glu Asp Met Leu Thr Val Trp 3290 3295 3300	10003
aac agg gtg tgg ata gag gac aat cca tgg atg gaa gac aaa act cca Asn Arg Val Trp Ile Glu Asp Asn Pro Trp Met Glu Asp Lys Thr Pro 3305 3310 3315	10051
gtc aca acg tgg gaa gat gtt cca tat cta ggg aag aga gaa gac caa Val Thr Thr Trp Glu Asp Val Pro Tyr Leu Gly Lys Arg Glu Asp Gln 3320 3325 3330 3335	10099
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260

aac ata ctc aca gca atc caa cag gtg aga agc ctc ata ggc aat gaa 10195
 Asn Ile Leu Thr Ala Ile Gln Gln Val Arg Ser Leu Ile Gly Asn Glu
 3355 3360 3365

gag ttt ctg gac tac atg cct tgg atg aag aga ttc agg aag gag gag 10243
 Glu Phe Leu Asp Tyr Met Pro Ser Met Lys Arg Phe Arg Lys Glu Glu
 3370 3375 3380

gag tca gag gga gcc att tgg taa aagcaggagg taaactgtca ggccacatta 10297
 Glu Ser Glu Gly Ala Ile Trp *
 3385 3390

agccacagta cggaagaagc tgtgcagcct gtgagcccg tccaaggagc ttaaaagaag 10357
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<210> 22

<211> 3390

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
 synthetic construct

<400> 22

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 1 5 10 15
 Lys Arg Val Arg Asn Arg Val Ser Thr Gly Ser Gln Leu Ala Lys Arg
 20 25 30
 Phe Ser Arg Gly Leu Leu Asn Gly Gln Gly Pro Met Lys Leu Val Met
 35 40 45
 Ala Phe Ile Ala Phe Leu Arg Phe Leu Ala Ile Pro Pro Thr Ala Gly
 50 55 60
 Val Leu Ala Arg Trp Gly Thr Phe Lys Lys Ser Gly Ala Ile Lys Val
 65 70 75 80
 Leu Lys Gly Phe Lys Lys Glu Ile Ser Asn Met Leu Ser Ile Ile Asn
 85 90 95
 Lys Arg Lys Lys Thr Ser Leu Cys Leu Met Met Met Leu Pro Ala Thr
 100 105 110
 Leu Ala Phe His Leu Thr Ser Arg Asp Gly Glu Pro Arg Met Ile Val
 115 120 125
 Gly Lys Asn Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ala Ser Gly
 130 135 140
 Ile Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Met Cys Asp
 145 150 155 160
 Asp Thr Val Thr Tyr Lys Cys Pro His Ile Thr Glu Val Glu Pro Glu
 165 170 175
 Asp Ile Asp Cys Trp Cys Asn Leu Thr Ser Thr Trp Val Thr Tyr Gly
 180 185 190

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Thr Cys Asn Gln Ala Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala
 195 200 205
 Leu Ala Pro His Val Gly Met Gly Leu Asp Thr Arg Thr Gln Thr Trp
 210 215 220
 Met Ser Ala Glu Gly Ala Trp Arg Gln Val Glu Lys Val Glu Thr Trp
 225 230 235 240
 Ala Leu Arg His Pro Gly Phe Thr Ile Leu Ala Leu Phe Leu Ala His
 245 250 255
 Tyr Ile Gly Thr Ser Leu Thr Gln Lys Val Val Ile Phe Ile Leu Leu
 260 265 270
 Met Leu Val Thr Pro Ser Met Thr Met Arg Cys Val Gly Val Gly Asn
 275 280 285
 Arg Asp Phe Val Glu Gly Leu Ser Gly Ala Thr Trp Val Asp Val Val
 290 295 300
 Leu Glu His Gly Gly Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr
 305 310 315 320
 Leu Asp Ile Glu Leu Gln Lys Thr Glu Ala Thr Gln Leu Ala Thr Leu
 325 330 335
 Arg Lys Leu Cys Ile Glu Gly Lys Ile Thr Asn Ile Thr Thr Asp Ser
 340 345 350
 Arg Cys Pro Thr Gln Gly Glu Ala Ile Leu Pro Glu Glu Gln Asp Gln
 355 360 365
 Asn Tyr Val Cys Lys His Thr Tyr Val Asp Arg Gly Trp Gly Asn Gly
 370 375 380
 Cys Gly Leu Phe Gly Lys Gly Ser Leu Val Thr Cys Ala Lys Phe Gln
 385 390 395 400
 Cys Leu Glu Ser Ile Glu Gly Lys Val Val Gln His Glu Asn Leu Lys
 405 410 415
 Tyr Thr Val Ile Ile Thr Val His Thr Gly Asp Gln His Gln Val Gly
 420 425 430
 Asn Glu Thr Gln Gly Val Thr Ala Glu Ile Thr Pro Gln Ala Ser Thr
 435 440 445
 Ala Glu Ala Ile Leu Pro Glu Tyr Gly Thr Leu Gly Leu Glu Cys Ser
 450 455 460
 Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Ile Leu Leu Thr Met Lys
 465 470 475 480
 Asn Lys Ala Trp Met Val His Arg Gln Trp Phe Phe Asp Leu Pro Leu
 485 490 495
 Pro Trp Thr Ser Gly Ala Thr Ala Glu Thr Pro Thr Trp Asn Arg Lys
 500 505 510
 Glu Leu Leu Val Thr Phe Lys Asn Ala His Ala Lys Lys Gln Glu Val
 515 520 525
 Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu Thr Gly
 530 535 540
 Ala Thr Glu Ile Gln Thr Ser Gly Gly Thr Ser Ile Phe Ala Gly His
 545 550 555 560
 Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Glu Leu Lys Gly Met Ser
 565 570 575
 Tyr Ala Met Cys Leu Gly Ser Phe Val Leu Lys Lys Glu Val Ser Glu
 580 585 590
 Thr Gln His Gly Thr Ile Leu Ile Lys Val Glu Tyr Lys Gly Lys Asp
 595 600 605
 Ala Pro Cys Lys Ile Pro Phe Ser Thr Glu Asp Gly Gln Gly Lys Ala
 610 615 620

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His	Asn	Gly	Arg	Leu	Ile	Thr	Ala	Asn	Pro	Val	Val	Thr	Lys	Lys	Glu	625	630	635	640
Glu	Pro	Val	Asn	Ile	Glu	Ala	Glu	Pro	Pro	Phe	Gly	Glu	Ser	Asn	Ile	645	650	655	660
Val	Ile	Gly	Ile	Gly	Asp	Lys	Ala	Leu	Lys	Ile	Asn	Trp	Tyr	Lys	Lys	660	665	670	675
Gly	Ser	Ser	Ile	Gly	Lys	Met	Phe	Glu	Ala	Thr	Ala	Arg	Gly	Ala	Arg	675	680	685	690
Arg	Met	Ala	Ile	Leu	Gly	Asp	Thr	Ala	Trp	Asp	Phe	Gly	Ser	Val	Gly	690	695	700	705
Gly	Val	Leu	Asn	Ser	Leu	Gly	Lys	Met	Val	His	Gln	Ile	Phe	Gly	Ser	710	715	720	725
Ala	Tyr	Thr	Ala	Leu	Phe	Gly	Gly	Val	Ser	Trp	Met	Met	Lys	Ile	Gly	725	730	735	740
Ile	Gly	Val	Leu	Leu	Thr	Trp	Ile	Gly	Leu	Asn	Ser	Lys	Asn	Thr	Ser	740	745	750	755
Met	Ser	Phe	Ser	Cys	Ile	Ala	Ile	Gly	Ile	Ile	Thr	Leu	Tyr	Leu	Gly	755	760	765	770
Ala	Val	Val	Gln	Ala	Asp	Met	Gly	Cys	Val	Ile	Asn	Trp	Lys	Gly	Lys	770	775	780	785
Glu	Leu	Lys	Cys	Gly	Ser	Gly	Ile	Phe	Val	Thr	Asn	Glu	Val	His	Thr	790	795	800	805
Trp	Thr	Glu	Gln	Tyr	Lys	Phe	Gln	Ala	Asp	Ser	Pro	Lys	Arg	Leu	Ala	810	815	820	825
Thr	Ala	Ile	Ala	Gly	Ala	Trp	Glu	Asn	Gly	Val	Cys	Gly	Ile	Arg	Ser	820	825	830	835
Thr	Thr	Arg	Met	Glu	Asn	Leu	Leu	Trp	Lys	Gln	Ile	Ala	Asn	Glu	Leu	840	845	850	855
Asn	Tyr	Ile	Leu	Trp	Glu	Asn	Asn	Ile	Lys	Leu	Thr	Val	Val	Val	Gly	860	865	870	875
Asp	Ile	Thr	Gly	Val	Leu	Glu	Gln	Gly	Lys	Arg	Thr	Leu	Thr	Pro	Gln	880	885	890	895
Pro	Met	Glu	Leu	Lys	Tyr	Ser	Trp	Lys	Thr	Trp	Gly	Lys	Ala	Lys	Ile	900	905	910	915
Val	Thr	Ala	Glu	Thr	Gln	Asn	Ser	Ser	Phe	Ile	Ile	Asp	Gly	Pro	Ser	920	925	930	935
Thr	Pro	Glu	Cys	Pro	Ser	Ala	Ser	Arg	Ala	Trp	Asn	Val	Trp	Glu	Val	940	945	950	955
Glu	Asp	Tyr	Gly	Phe	Gly	Val	Phe	Thr	Thr	Asn	Ile	Trp	Leu	Lys	Leu	960	965	970	975
Arg	Glu	Val	Tyr	Thr	Gln	Leu	Cys	Asp	His	Arg	Leu	Met	Ser	Ala	Ala	980	985	990	995
Val	Lys	Asp	Glu	Arg	Ala	Val	His	Ala	Asp	Met	Gly	Tyr	Trp	Ile	Glu	1000	1005	1010	1015
Ser	Gln	Lys	Asn	Gly	Ser	Trp	Lys	Leu	Glu	Lys	Ala	Ser	Phe	Ile	Glu	1020	1025	1030	1035
Val	Lys	Thr	Cys	Thr	Trp	Pro	Lys	Ser	His	Thr	Leu	Trp	Ser	Asn	Gly	1040	1045	1050	1055
Val	Leu	Glu	Ser	Asp	Met	Ile	Ile	Pro	Lys	Ser	Leu	Ala	Gly	Pro	Ile	1060	1065	1070	1075
Ser	Gln	His	Asn	His	Arg	Pro	Gly	Tyr	His	Thr	Gln	Thr	Ala	Gly	Pro	1080	1085	1090	1095
Trp	His	Leu	Gly	Lys	Leu	Glu	Leu	Asp	Phe	Asn	Tyr	Cys	Glu	Gly	Thr	1100	1105	1110	1115

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Thr Val Val Ile Ser Glu Asn Cys Gly Thr Arg Gly Pro Ser Leu Arg
 1060 1065 1070
 Thr Thr Thr Val Ser Gly Lys Leu Ile His Glu Trp Cys Cys Arg Ser
 1075 1080 1085
 Cys Thr Leu Pro Pro Leu Arg Tyr Met Gly Glu Asp Gly Cys Trp Tyr
 1090 1095 1100
 Gly Met Glu Ile Arg Pro Ile Asn Glu Lys Glu Glu Asn Met Val Lys
 1105 1110 1115 1120
 Ser Leu Ala Ser Ala Gly Ser Gly Lys Val Asp Asn Phe Thr Met Gly
 1125 1130 1135
 Val Leu Cys Leu Ala Ile Leu Phe Glu Glu Val Met Arg Gly Lys Phe
 1140 1145 1150
 Gly Lys Lys His Met Ile Ala Gly Val Leu Phe Thr Phe Val Leu Leu
 1155 1160 1165
 Leu Ser Gly Gln Ile Thr Trp Arg Asp Met Ala His Thr Leu Ile Met
 1170 1175 1180
 Ile Gly Ser Asn Ala Ser Asp Arg Met Gly Met Gly Val Thr Tyr Leu
 1185 1190 1195 1200
 Ala Leu Ile Ala Thr Phe Lys Ile Gln Pro Leu Leu Ala Leu Gly Phe
 1205 1210 1215
 Phe Leu Arg Lys Leu Thr Ser Arg Glu Asn Leu Leu Leu Gly Val Gly
 1220 1225 1230
 Leu Ala Met Ala Ala Thr Leu Arg Leu Pro Glu Asp Ile Glu Gln Met
 1235 1240 1245
 Ala Asn Gly Ile Ala Leu Gly Leu Met Ala Leu Lys Leu Ile Thr Gln
 1250 1255 1260
 Phe Glu Thr Tyr Gln Leu Trp Thr Ala Leu Val Ser Leu Thr Cys Ser
 1265 1270 1275 1280
 Asn Thr Ile Phe Thr Leu Thr Val Ala Trp Arg Thr Ala Thr Leu Ile
 1285 1290 1295
 Leu Ala Gly Ile Ser Leu Leu Pro Val Cys Gln Ser Ser Ser Met Arg
 1300 1305 1310
 Lys Thr Asp Trp Leu Pro Met Thr Val Ala Ala Met Gly Ala Gln Pro
 1315 1320 1325
 Leu Pro Leu Phe Ile Phe Ser Leu Lys Asp Thr Leu Lys Arg Arg Ser
 1330 1335 1340
 Trp Pro Leu Asn Glu Gly Val Met Ala Val Gly Leu Val Ser Ile Leu
 1345 1350 1355 1360
 Ala Ser Ser Leu Leu Arg Asn Asp Val Pro Met Ala Gly Pro Leu Val
 1365 1370 1375
 Ala Gly Gly Leu Leu Ile Ala Cys Tyr Val Ile Thr Gly Thr Ser Ala
 1380 1385 1390
 Asp Leu Thr Val Glu Lys Ala Ala Asp Val Thr Trp Glu Glu Glu Ala
 1395 1400 1405
 Glu Gln Thr Gly Val Ser His Asn Leu Met Val Thr Val Asp Asp Asp
 1410 1415 1420
 Gly Thr Met Arg Ile Lys Asp Asp Glu Thr Glu Asn Ile Leu Thr Val
 1425 1430 1435 1440
 Leu Leu Lys Thr Ala Leu Leu Ile Val Ser Gly Ile Phe Pro Tyr Ser
 1445 1450 1455
 Ile Pro Ala Thr Leu Leu Val Trp His Thr Trp Gln Lys Gln Thr Gln
 1460 1465 1470
 Arg Ser Gly Val Leu Trp Asp Val Pro Ser Pro Pro Glu Thr Gln Lys
 1475 1480 1485

264

Ala Glu Leu Glu Glu Gly Val Tyr Arg Ile Lys Gln Gln Gly Ile Phe
 1490 1495 1500
 Gly Lys Thr Gln Val Gly Val Gly Val Gln Lys Glu Gly Val Phe His
 1505 1510 1515 1520
 Thr Met Trp His Val Thr Arg Gly Ala Val Leu Thr His Asn Gly Lys
 1525 1530 1535
 Arg Leu Glu Pro Asn Trp Ala Ser Val Lys Lys Asp Leu Ile Ser Tyr
 1540 1545 1550
 Gly Gly Gly Trp Arg Leu Ser Ala Gln Trp Lys Lys Gly Glu Glu Val
 1555 1560 1565
 Gln Val Ile Ala Val Glu Pro Gly Lys Asn Pro Lys Asn Phe Gln Thr
 1570 1575 1580
 Met Pro Gly Ile Phe Gln Thr Thr Thr Gly Glu Ile Gly Ala Ile Ala
 1585 1590 1595 1600
 Leu Asp Phe Lys Pro Gly Thr Ser Gly Ser Pro Ile Ile Asn Arg Glu
 1605 1610 1615
 Gly Lys Val Val Gly Leu Tyr Gly Asn Gly Val Val Thr Lys Asn Gly
 1620 1625 1630
 Gly Tyr Val Ser Gly Ile Ala Gln Thr Asn Ala Glu Pro Asp Gly Pro
 1635 1640 1645
 Thr Pro Glu Leu Glu Glu Glu Met Phe Lys Lys Arg Asn Leu Thr Ile
 1650 1655 1660
 Met Asp Leu His Pro Gly Ser Gly Lys Thr Arg Lys Tyr Leu Pro Ala
 1665 1670 1675 1680
 Ile Val Arg Glu Ala Ile Lys Arg Arg Leu Arg Thr Leu Ile Leu Ala
 1685 1690 1695
 Pro Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Lys Gly Leu
 1700 1705 1710
 Pro Ile Arg Tyr Gln Thr Thr Ala Thr Lys Ser Glu His Thr Gly Arg
 1715 1720 1725
 Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg Leu Leu
 1730 1735 1740
 Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu Ala
 1745 1750 1755 1760
 His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser Thr
 1765 1770 1775
 Arg Val Gly Met Gly Glu Ala Ala Ala Ile Phe Met Thr Ala Thr Pro
 1780 1785 1790
 Pro Gly Thr Ala Asp Ala Phe Pro Gln Ser Asn Ala Pro Ile Gln Asp
 1795 1800 1805
 Glu Glu Arg Asp Ile Pro Glu Arg Ser Trp Asn Ser Gly Asn Glu Trp
 1810 1815 1820
 Ile Thr Asp Phe Val Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys
 1825 1830 1835 1840
 Ala Gly Asn Asp Ile Ala Asn Cys Leu Arg Lys Asn Gly Lys Lys Val
 1845 1850 1855
 Ile Gln Leu Ser Arg Lys Thr Phe Asp Thr Glu Tyr Gln Lys Thr Lys
 1860 1865 1870
 Leu Asn Asp Trp Asp Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly
 1875 1880 1885
 Ala Asn Phe Lys Ala Asp Arg Val Ile Asp Pro Arg Arg Cys Leu Lys
 1890 1895 1900
 Pro Val Ile Leu Thr Asp Gly Pro Glu Arg Val Ile Leu Ala Gly Pro
 1905 1910 1915 1920

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Met Pro Val Thr Val Ala Ser Ala Ala Gln Arg Arg Gly Arg Val Gly
 1925 1930 1935
 Arg Asn Pro Gln Lys Glu Asn Asp Gln Tyr Ile Phe Met Gly Gln Pro
 1940 1945 1950
 Leu Asn Asn Asp Glu Asp His Ala His Trp Thr Glu Ala Lys Met Leu
 1955 1960 1965
 Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ala Leu Phe Glu
 1970 1975 1980
 Pro Glu Arg Glu Lys Ser Ala Ala Ile Asp Gly Glu Tyr Arg Leu Lys
 1985 1990 1995 2000
 Gly Glu Ser Arg Lys Thr Phe Val Glu Leu Met Arg Arg Gly Asp Leu
 2005 2010 2015
 Pro Val Trp Leu Ala His Lys Val Ala Ser Glu Gly Ile Lys Tyr Thr
 2020 2025 2030
 Asp Arg Lys Trp Cys Phe Asp Gly Glu Arg Asn Asn Gln Ile Leu Glu
 2035 2040 2045
 Glu Asn Met Asp Val Glu Ile Trp Thr Lys Glu Gly Glu Lys Lys Lys
 2050 2055 2060
 Leu Arg Pro Arg Trp Leu Asp Ala Arg Thr Tyr Ser Asp Pro Leu Ala
 2065 2070 2075 2080
 Leu Lys Glu Phe Lys Asp Phe Ala Ala Gly Arg Lys Ser Ile Ala Leu
 2085 2090 2095
 Asp Leu Val Thr Glu Ile Gly Arg Val Pro Ser His Leu Ala His Arg
 2100 2105 2110
 Thr Arg Asn Ala Leu Asp Asn Leu Val Met Leu His Thr Ser Glu His
 2115 2120 2125
 Gly Gly Arg Ala Tyr Arg His Ala Val Glu Glu Leu Pro Glu Thr Met
 2130 2135 2140
 Glu Thr Leu Leu Leu Leu Gly Leu Met Ile Leu Leu Thr Gly Gly Ala
 2145 2150 2155 2160
 Met Leu Phe Leu Ile Ser Gly Lys Gly Ile Gly Lys Thr Ser Ile Gly
 2165 2170 2175
 Leu Ile Cys Val Ile Ala Ser Ser Gly Met Leu Trp Met Ala Asp Val
 2180 2185 2190
 Pro Leu Gln Trp Ile Ala Ser Ala Ile Val Leu Glu Phe Phe Met Met
 2195 2200 2205
 Val Leu Leu Ile Pro Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn
 2210 2215 2220
 Gln Leu Ala Tyr Val Val Ile Gly Ile Leu Thr Leu Ala Ala Ile Val
 2225 2230 2235 2240
 Ala Ala Asn Glu Met Gly Leu Leu Glu Thr Thr Lys Arg Asp Leu Gly
 2245 2250 2255
 Met Ser Lys Glu Pro Gly Val Val Ser Pro Thr Ser Tyr Leu Asp Val
 2260 2265 2270
 Asp Leu His Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr
 2275 2280 2285
 Val Ile Thr Pro Met Leu Arg His Thr Ile Glu Asn Ser Thr Ala Asn
 2290 2295 2300
 Val Ser Leu Ala Ala Ile Ala Asn Gln Ala Val Val Leu Met Gly Leu
 2305 2310 2315 2320
 Asp Lys Gly Trp Pro Ile Ser Lys Met Asp Leu Gly Val Pro Leu Leu
 2325 2330 2335
 Ala Leu Gly Cys Tyr Ser Gln Val Asn Pro Leu Thr Leu Ala Ala Ala
 2340 2345 2350

266

Val Leu Leu Leu Val Thr His Tyr Ala Ile Ile Gly Pro Gly Leu Gln
 2355 2360 2365
 Ala Lys Ala Thr Arg Glu Ala Gln Lys Arg Thr Ala Ala Gly Ile Met
 2370 2375 2380
 Lys Asn Pro Thr Val Asp Gly Ile Met Thr Ile Asp Leu Asp Pro Val
 2385 2390 2395 2400
 Ile Tyr Asp Ser Lys Phe Glu Lys Gln Leu Gly Gln Val Met Leu Leu
 2405 2410 2415
 Val Leu Cys Ala Val Gln Leu Leu Leu Met Arg Thr Ser Trp Ala Leu
 2420 2425 2430
 Cys Glu Val Leu Thr Leu Ala Thr Gly Pro Ile Thr Thr Leu Trp Glu
 2435 2440 2445
 Gly Ser Pro Gly Lys Phe Trp Asn Thr Thr Ile Ala Val Ser Met Ala
 2450 2455 2460
 Asn Ile Phe Arg Gly Ser Tyr Leu Ala Gly Ala Gly Leu Ala Phe Ser
 2465 2470 2475 2480
 Ile Met Lys Ser Val Gly Thr Gly Lys Arg Gly Thr Gly Ser Gln Gly
 2485 2490 2495
 Glu Thr Leu Gly Glu Lys Trp Lys Lys Lys Leu Asn Gln Leu Ser Arg
 2500 2505 2510
 Lys Glu Phe Asp Leu Tyr Lys Lys Ser Gly Ile Thr Glu Val Asp Arg
 2515 2520 2525
 Thr Glu Ala Lys Glu Gly Leu Lys Arg Gly Glu Ile Thr His His Ala
 2530 2535 2540
 Val Ser Arg Gly Ser Ala Lys Leu Gln Trp Phe Val Glu Arg Asn Met
 2545 2550 2555 2560
 Val Ile Pro Glu Gly Arg Val Ile Asp Leu Gly Cys Gly Arg Gly Gly
 2565 2570 2575
 Trp Ser Tyr Tyr Cys Ala Gly Leu Lys Lys Val Thr Glu Val Arg Gly
 2580 2585 2590
 Tyr Thr Lys Gly Gly Pro Gly His Glu Glu Pro Val Pro Met Ser Thr
 2595 2600 2605
 Tyr Gly Trp Asn Ile Val Lys Leu Met Ser Gly Lys Asp Val Phe Tyr
 2610 2615 2620
 Leu Pro Pro Glu Lys Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser
 2625 2630 2635
 Ser Pro Ser Pro Thr Val Glu Glu Ser Arg Thr Ile Arg Val Leu Lys
 2645 2650 2655
 Met Val Glu Pro Trp Leu Lys Asn Asn Gln Phe Cys Ile Lys Val Leu
 2660 2665 2670
 Asn Pro Tyr Met Pro Thr Val Ile Glu His Leu Glu Arg Leu Gln Arg
 2675 2680 2685
 Lys His Gly Gly Met Leu Val Arg Asn Pro Leu Ser Arg Asn Ser Thr
 2690 2695 2700
 His Glu Met Tyr Trp Ile Ser Asn Gly Thr Gly Asn Ile Val Ser Ser
 2705 2710 2715 2720
 Val Asn Met Val Ser Arg Leu Leu Leu Asn Arg Phe Thr Met Thr His
 2725 2730 2735
 Arg Arg Pro Thr Ile Glu Lys Asp Val Asp Leu Gly Ala Gly Thr Arg
 2740 2745 2750
 His Val Asn Ala Glu Pro Glu Thr Pro Asn Met Asp Val Ile Gly Glu
 2755 2760 2765
 Arg Ile Lys Arg Ile Lys Glu Glu His Ser Ser Thr Trp His Tyr Asp
 2770 2775 2780

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Asp	Glu	Asn	Pro	Tyr	Lys	Thr	Trp	Ala	Tyr	His	Gly	Ser	Tyr	Glu	Val	2785	2790	2795	2800
Lys	Ala	Thr	Gly	Ser	Ala	Ser	Ser	Met	Ile	Asn	Gly	Val	Val	Lys	Leu	2805	2810		2815
Leu	Thr	Lys	Pro	Trp	Asp	Val	Val	Pro	Met	Val	Thr	Gln	Met	Ala	Met	2820	2825		2830
Thr	Asp	Thr	Thr	Pro	Phe	Gly	Gln	Gln	Arg	Val	Phe	Lys	Glu	Lys	Val	2835	2840		2845
Asp	Thr	Arg	Thr	Pro	Arg	Pro	Met	Pro	Gly	Thr	Arg	Lys	Val	Met	Glu	2850	2855	2860	
Ile	Thr	Ala	Glu	Trp	Leu	Trp	Arg	Thr	Leu	Gly	Arg	Asn	Lys	Arg	Pro	2865	2870	2875	2880
Arg	Leu	Cys	Thr	Arg	Glu	Glu	Phe	Thr	Lys	Lys	Val	Arg	Thr	Asn	Ala	2885	2890		2895
Ala	Met	Gly	Ala	Val	Phe	Thr	Glu	Glu	Asn	Gln	Trp	Asp	Ser	Ala	Arg	2900	2905		2910
Ala	Ala	Val	Glu	Asp	Glu	Glu	Phe	Trp	Lys	Leu	Val	Asp	Arg	Glu	Arg	2915	2920		2925
Glu	Leu	His	Lys	Leu	Gly	Lys	Cys	Gly	Ser	Cys	Val	Tyr	Asn	Met	Met	2930	2935	2940	
Gly	Lys	Arg	Glu	Lys	Lys	Leu	Gly	Glu	Phe	Gly	Lys	Ala	Lys	Gly	Ser	2945	2950	2955	2960
Arg	Ala	Ile	Trp	Tyr	Met	Trp	Leu	Gly	Ala	Arg	Tyr	Leu	Glu	Phe	Glu	2965	2970		2975
Ala	Leu	Gly	Phe	Leu	Asn	Glu	Asp	His	Trp	Phe	Ser	Arg	Glu	Asn	Ser	2980	2985		2990
Tyr	Ser	Gly	Val	Glu	Gly	Glu	Gly	Leu	His	Lys	Leu	Gly	Tyr	Ile	Leu	2995	3000		3005
Arg	Asp	Ile	Ser	Lys	Ile	Pro	Gly	Gly	Ala	Met	Tyr	Ala	Asp	Asp	Thr	3010	3015	3020	
Ala	Gly	Trp	Asp	Thr	Arg	Ile	Thr	Glu	Asp	Asp	Leu	His	Asn	Glu	Glu	3025	3030	3035	3040
Lys	Ile	Thr	Gln	Gln	Met	Asp	Pro	Glu	His	Arg	Gln	Leu	Ala	Asn	Ala	3045	3050		3055
Ile	Phe	Lys	Leu	Thr	Tyr	Gln	Asn	Lys	Val	Val	Lys	Val	Gln	Arg	Pro	3060	3065		3070
Thr	Pro	Lys	Gly	Thr	Val	Met	Asp	Ile	Ile	Ser	Arg	Lys	Asp	Gln	Arg	3075	3080		3085
Gly	Ser	Gly	Gln	Val	Gly	Thr	Tyr	Gly	Leu	Asn	Thr	Phe	Thr	Asn	Met	3090	3095	3100	
Glu	Ala	Gln	Leu	Ile	Arg	Gln	Met	Glu	Gly	Glu	Gly	Val	Leu	Ser	Lys	3105	3110	3115	3120
Ala	Asp	Leu	Glu	Asn	Pro	His	Pro	Leu	Glu	Lys	Lys	Ile	Thr	Gln	Trp	3125	3130		3135
Leu	Glu	Thr	Lys	Gly	Val	Glu	Arg	Leu	Lys	Arg	Met	Ala	Ile	Ser	Gly	3140	3145		3150
Asp	Asp	Cys	Val	Val	Lys	Pro	Ile	Asp	Asp	Arg	Phe	Ala	Asn	Ala	Leu	3155	3160	3165	
Leu	Ala	Leu	Asn	Asp	Met	Gly	Lys	Val	Arg	Lys	Asp	Ile	Pro	Gln	Trp	3170	3175	3180	
Gln	Pro	Ser	Lys	Gly	Trp	His	Asp	Trp	Gln	Gln	Val	Pro	Phe	Cys	Ser	3185	3190	3195	3200
His	His	Phe	His	Glu	Leu	Ile	Met	Lys	Asp	Gly	Arg	Lys	Leu	Val	Val	3205	3210		3215

268

Pro Cys Arg Pro Gln Asp Glu Leu Ile Gly Arg Ala Arg Ile Ser Gln
 3220 3225 3230
 Gly Ala Gly Trp Ser Leu Arg Glu Thr Ala Cys Leu Gly Lys Ala Tyr
 3235 3240 3245
 Ala Gln Met Trp Ala Leu Met Tyr Phe His Arg Arg Asp Leu Arg Leu
 3250 3255 3260
 Ala Ser Asn Ala Ile Cys Ser Ala Val Pro Val His Trp Val Pro Thr
 3265 3270 3275 3280
 Ser Arg Thr Thr Trp Ser Ile His Ala His His Gln Trp Met Thr Thr
 3285 3290 3295
 Glu Asp Met Leu Thr Val Trp Asn Arg Val Trp Ile Glu Asp Asn Pro
 3300 3305 3310
 Trp Met Glu Asp Lys Thr Pro Val Thr Thr Trp Glu Asp Val Pro Tyr
 3315 3320 3325
 Leu Gly Lys Arg Glu Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr
 3330 3335 3340
 Ser Arg Ala Thr Trp Ala Gln Asn Ile Leu Thr Ala Ile Gln Gln Val
 3345 3350 3355 3360
 Arg Ser Leu Ile Gly Asn Glu Glu Phe Leu Asp Tyr Met Pro Ser Met
 3365 3370 3375
 Lys Arg Phe Arg Lys Glu Glu Glu Ser Glu Gly Ala Ile Trp
 3380 3385 3390

<210> 23

<211> 10648

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
 synthetic construct

<221> CDS

<222> (102)...(10265)

<400> 23

agttgttagt ctgtgtggac cgacaaggac agttccaaat cggaagcttg cttaacacag 60
 ttctaacagt ttgtttgaat agagagcaga tctctggaaa a atg aac caa cga aaa 116
 Met Asn Gln Arg Lys
 1 5
 aag gtg gtt aga cca cct ttc aat atg ctg aaa cgc gag aga aac cgc 164
 Lys Val Val Arg Pro Pro Phe Asn Met Leu Lys Arg Glu Arg Asn Arg
 10 15 20
 gta tca acc cct caa ggg ttg gtg aag aga ttc tca acc gga ctt ttt 212
 Val Ser Thr Pro Gln Gly Leu Val Lys Arg Phe Ser Thr Gly Leu Phe
 25 30 35
 tct ggg aaa gga ccc tta cgg atg gtg cta gca ttc atc acg ttt ttg 260
 Ser Gly Lys Gly Pro Leu Arg Met Val Leu Ala Phe Ile Thr Phe Leu
 40 45 50

269

cga gtc ctt tcc atc cca cca aca gca ggg att ctg aaa aga tgg gga	308
Arg Val Leu Ser Ile Pro Thr Ala Gly Ile Leu Lys Arg Trp Gly	
55 60 65	
cag ttg aag aaa aat aag gcc atc agg ata ctg att gga ttc agg aag	356
Gln Leu Lys Lys Asn Lys Ala Ile Arg Ile Leu Ile Gly Phe Arg Lys	
70 75 80 85	
gag ata ggc cgc atg ctg aac atc ttg aac ggg aga aaa agg tca acg	404
Glu Ile Gly Arg Met Leu Asn Ile Leu Asn Gly Arg Lys Arg Ser Thr	
90 95 100	
ata aca ttg ctg tgc ttg att ccc acc gta atg gcg ttt cac ttg tca	452
Ile Thr Leu Leu Cys Leu Ile Pro Thr Val Met Ala Phe His Leu Ser	
105 110 115	
aca aga gat ggc gaa ccc ctc atg ata gtg gca aaa cat gaa agg ggg	500
Thr Arg Asp Gly Glu Pro Leu Met Ile Val Ala Lys His Glu Arg Gly	
120 125 130	
aga cct ctc ttg ttt aag aca aca gag ggg atc aac aaa tgc act ctc	548
Arg Pro Leu Leu Phe Lys Thr Thr Glu Gly Ile Asn Lys Cys Thr Leu	
135 140 145	
att gcc atg gac ttg ggt gaa atg tgt gag gac act gtc acg tat aaa	596
Ile Ala Met Asp Leu Gly Glu Met Cys Glu Asp Thr Val Thr Tyr Lys	
150 155 160 165	
tgc ccc tta ctg gtc aat acc gaa cct gaa gac att gat tgc tgg tgc	644
Cys Pro Leu Leu Val Asn Thr Glu Pro Glu Asp Ile Asp Cys Trp Cys	
170 175 180	
aat ctc acg tct acc tgg gtc atg tat ggg aca tgc acc cag agc gga	692
Asn Leu Thr Ser Thr Trp Val Met Tyr Gly Thr Cys Thr Gln Ser Gly	
185 190 195	
gaa cgg aga cga gag aag cgc tca gta gct tta aca cca cat tca gga	740
Glu Arg Arg Arg Glu Lys Arg Ser Val Ala Leu Thr Pro His Ser Gly	
200 205 210	
atg gga ttg gaa aca aga gct gag aca tgg atg tca tgc gaa ggg gct	788
Met Gly Leu Glu Thr Arg Ala Glu Thr Trp Met Ser Ser Glu Gly Ala	
215 220 225	
tgg aag cat gct cag aga gta gag agc tgg ata ctc aga aac cca gga	836
Trp Lys His Ala Gln Arg Val Glu Ser Trp Ile Leu Arg Asn Pro Gly	
230 235 240 245	
ttc gcg ctc ttg gca gga ttt atg gct tat atg att ggg caa aca gga	884
Phe Ala Leu Leu Ala Gly Phe Met Ala Tyr Met Ile Gly Gln Thr Gly	
250 255 260	
atc cag cga act gtc ttc ttt gtc cta atg atg ctg gtc gcc cca tcc	932
Ile Gln Arg Thr Val Phe Phe Val Leu Met Met Leu Val Ala Pro Ser	
265 270 275	

270

tac gga atg cga tgc gta gga gta gga aac aga gac ttt gtg gaa gga Tyr Gly Met Arg Cys Val Gly Val Gly Asn Arg Asp Phe Val Glu Gly	980
280 285 290	
gtc tca ggt gga gca tgg gtc gat ctg gtg cta gaa cat gga gga tgc Val Ser Gly Gly Ala Trp Val Asp Leu Val Leu Glu His Gly Gly Cys	1028
295 300 305	
gtc aca acc atg gcc cag gga aaa cca acc ttg gat ttt gaa ctg act Val Thr Thr Met Ala Gln Gly Lys Pro Thr Leu Asp Phe Glu Leu Thr	1076
310 315 320 325	
aag aca aca gcc aag gaa gtg gct ctg tta aga acc tat tgc att gaa Lys Thr Thr Ala Lys Glu Val Ala Leu Leu Arg Thr Tyr Cys Ile Glu	1124
330 335 340	
gcc tca ata tca aac ata acc acg gca aca aga tgt cca acg caa gga Ala Ser Ile Ser Asn Ile Thr Thr Ala Thr Arg Cys Pro Thr Gln Gly	1172
345 350 355	
gag cct tat cta aaa gag gaa caa gac caa cag tac att tgc cgg aga Glu Pro Tyr Leu Lys Glu Glu Gln Asp Gln Gln Tyr Ile Cys Arg Arg	1220
360 365 370	
gat gtg gta gac aga ggg tgg ggc aat ggc tgt ggc ttg ttt gga aaa Asp Val Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly Lys	1268
375 380 385	
gga gga gtt gtg aca tgt gcg aag ttt tca tgt tcg ggg aag ata aca Gly Gly Val Val Thr Cys Ala Lys Phe Ser Cys Ser Gly Lys Ile Thr	1316
390 395 400 405	
ggc aat ttg gtc caa att gag aac ctt gaa tac aca gtg gtt gta aca Gly Asn Leu Val Gln Ile Glu Asn Leu Glu Tyr Thr Val Val Val Thr	1364
410 415 420	
gtc cac aat gga gac acc cat gca gta gga aat gac aca tcc aat cat Val His Asn Gly Asp Thr His Ala Val Gly Asn Asp Thr Ser Asn His	1412
425 430 435	
gga gtt aca gcc acg ata act ccc agg tca cca tcg gtg gaa gtc aaa Gly Val Thr Ala Thr Ile Thr Pro Arg Ser Pro Ser Val Glu Val Lys	1460
440 445 450	
ttg ccg gac tat gga gaa cta aca ctc gat tgt gaa ccc agg tct gga Leu Pro Asp Tyr Gly Glu Leu Thr Leu Asp Cys Glu Pro Arg Ser Gly	1508
455 460 465	
att gac ttt aat gag atg att ctg atg aaa atg aaa aag aaa aca tgg Ile Asp Phe Asn Glu Met Ile Leu Met Lys Met Lys Lys Lys Thr Trp	1556
470 475 480 485	

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ctt gtg cat aag caa tgg ttt ttg gat cta cct cta cca tgg aca gca	1604
Leu Val His Lys Gln Trp Phe Leu Asp Leu Pro Leu Pro Trp Thr Ala	
490 495 500	
gga gca gac aca tca gag gtt cac tgg aat tac aaa gag aga atg gtg	1652
Gly Ala Asp Thr Ser Glu Val His Trp Asn Tyr Lys Glu Arg Met Val	
505 510 515	
aca ttt aag gtt cct cat gcc aag aga cag gat gtg aca gtg ctg gga	1700
Thr Phe Lys Val Pro His Ala Lys Arg Gln Asp Val Thr Val Leu Gly	
520 525 530	
tct cag gaa gga gcc atg cat tct gcc ctc gct gga gcc aca gaa gtg	1748
Ser Gln Glu Gly Ala Met His Ser Ala Leu Ala Gly Ala Thr Glu Val	
535 540 545	
gac tcc ggt gat gga aat cac atg ttt gca gga cat ctc aag tgc aaa	1796
Asp Ser Gly Asp Gly Asn His Met Phe Ala Gly His Leu Lys Cys Lys	
550 555 560 565	
gtc cgt atg gag aaa ttg aga atc aag gga atg tca tac acg atg tgt	1844
Val Arg Met Glu Lys Leu Arg Ile Lys Gly Met Ser Tyr Thr Met Cys	
570 575 580	
tca gga aag ttc tca att gac aaa gag atg gca gaa aca cag cat ggg	1892
Ser Gly Lys Phe Ser Ile Asp Lys Glu Met Ala Glu Thr Gln His Gly	
585 590 595	
aca aca gtg gtg aaa gtc aag tat gaa ggt gct gga gct ccg tgt aaa	1940
Thr Thr Val Val Lys Val Lys Tyr Glu Gly Ala Gly Ala Pro Cys Lys	
600 605 610	
gtc ccc ata gag ata aga gat gtg aac aag gaa aaa gtg gtt ggg cgt	1988
Val Pro Ile Glu Ile Arg Asp Val Asn Lys Glu Lys Val Val Gly Arg	
615 620 625	
atc atc tca tcc acc cct ttg gct gag aat acc aac agt gca acc aac	2036
Ile Ile Ser Ser Thr Pro Leu Ala Glu Asn Thr Asn Ser Ala Thr Asn	
630 635 640 645	
ata gag tta gaa ccc ccc ttt ggg gac agc tac ata gtg ata ggt gtt	2084
Ile Glu Leu Glu Pro Pro Phe Gly Asp Ser Tyr Ile Val Ile Gly Val	
650 655 660	
gga aac agt gca tta aca ctc cat tgg ttc agg aaa ggg agt tcc att	2132
Gly Asn Ser Ala Leu Thr Leu His Trp Phe Arg Lys Gly Ser Ser Ile	
665 670 675	
ggc aag atg ttt gag tcc aca tac aga ggt gca aaa cga atg gcc att	2180
Gly Lys Met Phe Glu Ser Thr Tyr Arg Gly Ala Lys Arg Met Ala Ile	
680 685 690	
cta ggt gaa aca gct tgg gat ttt ggt tcc gtt ggt gga ctg ttc aca	2228
Leu Gly Glu Thr Ala Trp Asp Phe Gly Ser Val Gly Gly Leu Phe Thr	
695 700 705	

272

tca ttg gga aag gct gtg cac cag gtt ttt gga agt gtg tat aca acc Ser Leu Gly Lys Ala Val His Gln Val Phe Gly Ser Val Tyr Thr Thr 710 715 720 725	2276
atg ttt gga gga gtc tca tgg atg att aga atc cta att ggg ttc cta Met Phe Gly Gly Val Ser Trp Met Ile Arg Ile Leu Ile Gly Phe Leu 730 735 740	2324
gtg ttg tgg att ggc acg aac tca agg aac act tca atg gct atg acg Val Leu Trp Ile Gly Thr Asn Ser Arg Asn Thr Ser Met Ala Met Thr 745 750 755	2372
tgc ata gct gtt gga gga atc act ctg ttt ctg ggc ttc aca gtt caa Cys Ile Ala Val Gly Gly Ile Thr Leu Phe Leu Gly Phe Thr Val Gln 760 765 770	2420
gca gac atg ggt tgt gtg gtg tca tgg agt ggg aaa gaa ttg aag tgt Ala Asp Met Gly Cys Val Val Ser Trp Ser Gly Lys Glu Leu Lys Cys 775 780 785	2468
gga agc gga att ttt gtg gtt gac aac gtg cac act tgg aca gaa cag Gly Ser Gly Ile Phe Val Val Asp Asn Val His Thr Trp Thr Glu Gln 790 795 800 805	2516
tac aaa ttt caa ccg gag tcc cca gcg aga cta gcg tct gca ata ttg Tyr Lys Phe Gln Pro Glu Ser Pro Ala Arg Leu Ala Ser Ala Ile Leu 810 815 820	2564
aat gcc cac aaa gat ggg gtc tgt gga att aga tca acc acg agg ctg Asn Ala His Lys Asp Gly Val Cys Gly Ile Arg Ser Thr Thr Arg Leu 825 830 835	2612
gaa aat gtc atg tgg aag caa ata acc aac gag cta aat tat gtt ctc Glu Asn Val Met Trp Lys Gln Ile Thr Asn Glu Leu Asn Tyr Val Leu 840 845 850	2660
tgg gaa gga gga cat gac ctc act gta gtg gct ggg gat gtg aag ggg Trp Glu Gly Gly His Asp Leu Thr Val Val Ala Gly Asp Val Lys Gly 855 860 865	2708
gtg ttg acc aaa ggc aag aga gca ctc aca ccc cca gtg aat gat ctg Val Leu Thr Lys Gly Lys Arg Ala Leu Thr Pro Pro Val Asn Asp Leu 870 875 880 885	2756
aaa tat tca tgg aag aca tgg gga aaa gca aaa atc ttc acc cca gaa Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala Lys Ile Phe Thr Pro Glu 890 895 900	2804
gca aga aat agc aca ttt tta ata gac gga cca gac acc tcc gaa tgc Ala Arg Asn Ser Thr Phe Leu Ile Asp Gly Pro Asp Thr Ser Glu Cys 905 910 915	2852

273

ccc aat gaa cga aga gca tgg aac ttt ctt gag gtg gaa gac tat gga Pro Asn Glu Arg Arg Ala Trp Asn Phe Leu Glu Val Glu Asp Tyr Gly 920 925 930	2900
ttt ggc atg ttc acg acc aac ata tgg atg aaa ttc cga gaa gga agt Phe Gly Met Phe Thr Thr Asn Ile Trp Met Lys Phe Arg Glu Gly Ser 935 940 945	2948
tca gaa gtg tgt gac cac agg tta atg tca gcg gca att aaa gat cag Ser Glu Val Cys Asp His Arg Leu Met Ser Ala Ala Ile Lys Asp Gln 950 955 960 965	2996
aaa gct gtg cat gct gac atg ggt tat tgg ata gag agc tca aaa aac Lys Ala Val His Ala Asp Met Gly Tyr Trp Ile Glu Ser Ser Lys Asn 970 975 980	3044
cag acc tgg cag ata gag aaa gca tct ctt att gaa gtg aaa aca tgt Gln Thr Trp Gln Ile Glu Lys Ala Ser Leu Ile Glu Val Lys Thr Cys 985 990 995	3092
ctg tgg ccc aag acc cac aca ttg tgg agc aat gga gtg ctg gaa agc Leu Trp Pro Lys Thr His Thr Leu Trp Ser Asn Gly Val Leu Glu Ser 1000 1005 1010	3140
cag atg ctc att cca aaa tca tat gcg ggc cct ttt tca cag cac aat Gln Met Leu Ile Pro Lys Ser Tyr Ala Gly Pro Phe Ser Gln His Asn 1015 1020 1025	3188
tac cgc cag ggc tat gcc acg caa acc gtg ggc cca tgg cac tta ggc Tyr Arg Gln Gly Tyr Ala Thr Gln Thr Val Gly Pro Trp His Leu Gly 1030 1035 1040 1045	3236
aaa tta gag ata gac ttt gga gaa tgc ccc gga aca aca gtc gca att Lys Leu Glu Ile Asp Phe Gly Glu Cys Pro Gly Thr Thr Val Ala Ile 1050 1055 1060	3284
cag gag gat tgt gac cat aga ggc cca tct ttg agg acc acc act gca Gln Glu Asp Cys Asp His Arg Gly Pro Ser Leu Arg Thr Thr Ala 1065 1070 1075	3332
tct gga aaa cta gtc acg caa tgg tgc tgc cgc tcc tgc acg atg cct Ser Gly Lys Leu Val Thr Gln Trp Cys Cys Arg Ser Cys Thr Met Pro 1080 1085 1090	3380
ccc tta agg ttc ttg gga gaa gat ggg tgc tgg tat ggg atg gag att Pro Leu Arg Phe Leu Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile 1095 1100 1105	3428
agg ccc ttg agt gaa aaa gaa gag aac atg gtc aaa tca cag gta acg Arg Pro Leu Ser Glu Lys Glu Glu Asn Met Val Lys Ser Gln Val Thr 1110 1115 1120 1125	3476
gcc gga cag ggc aca tca gaa act ttt tct atg ggt ctg ttg tgc ctg Ala Gly Gln Gly Thr Ser Glu Thr Phe Ser Met Gly Leu Leu Cys Leu 1130 1135 1140	3524

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acc ttg ttt gtg gaa gaa tgc ttg agg aga aga gtc act agg aaa cac	3572
Thr Leu Phe Val Glu Glu Cys Leu Arg Arg Val Thr Arg Lys His	
1145 1150 1155	
atg ata ttg gtt gtg gtg atc act ctt tgt gcc atc atc cta gga ggc	3620
Met Ile Leu Val Val Val Ile Thr Leu Cys Ala Ile Ile Leu Gly Gly	
1160 1165 1170	
ctc aca tgg atg gac tta cta cga gcc ctc atc atg ttg ggg gac act	3668
Leu Thr Trp Met Asp Leu Leu Arg Ala Leu Ile Met Leu Gly Asp Thr	
1175 1180 1185	
atg tct ggt aga ata gga gga cag atc cac cta gcc atc atg gca gtg	3716
Met Ser Gly Arg Ile Gly Gly Gln Ile His Leu Ala Ile Met Ala Val	
1190 1195 1200 1205	
ttc aag atg tca cca gga tac gtg ctg ggt gtg ttt tta agg aaa ctc	3764
Phe Lys Met Ser Pro Gly Tyr Val Leu Gly Val Phe Leu Arg Lys Leu	
1210 1215 1220	
act tca aga gag aca gca cta atg gta ata gga atg gcc atg aca acg	3812
Thr Ser Arg Glu Thr Ala Leu Met Val Ile Gly Met Ala Met Thr Thr	
1225 1230 1235	
gtg ctt tca att cca cat gac ctt atg gaa ctc att gat gga ata tca	3860
Val Leu Ser Ile Pro His Asp Leu Met Glu Leu Ile Asp Gly Ile Ser	
1240 1245 1250	
ctg ggg cta att ttg cta aaa ata gtg aca cat ttt gac aac acc caa	3908
Leu Gly Leu Ile Leu Leu Lys Ile Val Thr His Phe Asp Asn Thr Gln	
1255 1260 1265	
gtg gga acc tta gcc ctt tcc ttg acc ttc ata aga tca aca atg cca	3956
Val Gly Thr Leu Ala Leu Ser Leu Thr Phe Ile Arg Ser Thr Met Pro	
1270 1275 1280 1285	
ttg gtc atg gct tgg agg acc att atg gct gtg ttg ttt gtg gtc aca	4004
Leu Val Met Ala Trp Arg Thr Ile Met Ala Val Leu Phe Val Val Thr	
1290 1295 1300	
ctc att cct ttg tgc agg aca agc tgt ctt caa aaa cag tct cat tgg	4052
Leu Ile Pro Leu Cys Arg Thr Ser Cys Leu Gln Lys Gln Ser His Trp	
1305 1310 1315	
gta gaa ata aca gca ctc atc cta gga gcc caa gct ctg cca gtg tac	4100
Val Glu Ile Thr Ala Leu Ile Leu Gly Ala Gln Ala Leu Pro Val Tyr	
1320 1325 1330	
cta atg act ctt atg aaa gga gcc tca aga aga tct tgg cct ctt aac	4148
Leu Met Thr Leu Met Lys Gly Ala Ser Arg Arg Ser Trp Pro Leu Asn	
1335 1340 1345	

275

gag ggc ata atg gct gtg ggt ttg gtt agt ctc tta gga agc gct ctt Glu Gly Ile Met Ala Val Gly Leu Val Ser Leu Leu Gly Ser Ala Leu 1350 1355 1360 1365	4196
tta aag aat gat gtc cct tta gct ggc cca atg gtg gca gga ggc tta Leu Lys Asn Asp Val Pro Leu Ala Gly Pro Met Val Ala Gly Gly Leu 1370 1375 1380	4244
ctt ctg gcg gct tac gtg atg agt ggt agc tca gca gat ctg tca cta Leu Leu Ala Ala Tyr Val Met Ser Gly Ser Ser Ala Asp Leu Ser Leu 1385 1390 1395	4292
gag aag gcc gcc aat gtg cag tgg gat gaa atg gca gac ata aca ggc Glu Lys Ala Ala Asn Val Gln Trp Asp Glu Met Ala Asp Ile Thr Gly 1400 1405 1410	4340
tca agc cca atc ata gaa gtg aag cag gat gaa gat ggc tct ttc tcc Ser Ser Pro Ile Ile Glu Val Lys Gln Asp Glu Asp Gly Ser Phe Ser 1415 1420 1425	4388
ata cgg gac gtc gag gaa acc aat atg ata acc ctt ttg gtg aaa ctg Ile Arg Asp Val Glu Glu Thr Asn Met Ile Thr Leu Leu Val Lys Leu 1430 1435 1440 1445	4436
gca ctg ata aca gtg tca ggt ctc tac ccc ttg gca att cca gtc aca Ala Leu Ile Thr Val Ser Gly Leu Tyr Pro Leu Ala Ile Pro Val Thr 1450 1455 1460	4484
atg acc tta tgg tac atg tgg caa gtg aaa aca caa aga tca gga gcc Met Thr Leu Trp Tyr Met Trp Gln Val Lys Thr Gln Arg Ser Gly Ala 1465 1470 1475	4532
ctg tgg gac gtc ccc tca ccc gct gcc act caa aaa gcc gca ctg tct Leu Trp Asp Val Pro Ser Pro Ala Ala Thr Gln Lys Ala Ala Leu Ser 1480 1485 1490	4580
gaa gga gtg tac agg atc atg caa aga ggg tta ttt ggg aaa act cag Glu Gly Val Tyr Arg Ile Met Gln Arg Gly Leu Phe Gly Lys Thr Gln 1495 1500 1505	4628
gtt gga gta ggg ata cac atg gaa ggt gta ttt cac aca atg tgg cat Val Gly Val Gly Ile His Met Glu Gly Val Phe His Thr Met Trp His 1510 1515 1520 1525	4676
gta aca aga gga tca gtg atc tgc cat gag act ggg aga ttg gag cca Val Thr Arg Gly Ser Val Ile Cys His Glu Thr Gly Arg Leu Glu Pro 1530 1535 1540	4724
tct tgg gct gac gtc agg aat gac atg ata tca tac ggt ggg gga tgg Ser Trp Ala Asp Val Arg Asn Asp Met Ile Ser Tyr Gly Gly Gly Trp 1545 1550 1555	4772
aga ctt gga gac aaa tgg gac aaa gaa gaa gat gtt cag gtc ctc gcc Arg Leu Gly Asp Lys Trp Asp Lys Glu Glu Asp Val Gln Val Leu Ala 1560 1565 1570	4820

276

ata gaa cca gga aaa aat cct aaa cat gtc caa acg aaa ccc ggc ctt Ile Glu Pro Gly Lys Asn Pro Lys His Val Gln Thr Lys Pro Gly Leu 1575 1580 1585	4868
ttc aag acc cta act gga gaa att gga gca gta aca tta gat ttc aaa Phe Lys Thr Leu Thr Gly Glu Ile Gly Ala Val Thr Leu Asp Phe Lys 1590 1595 1600 1605	4916
ccc gga acg tct ggt tct ccc atc atc aac agg aaa gga aaa gtc atc Pro Gly Thr Ser Gly Ser Pro Ile Ile Asn Arg Lys Gly Lys Val Ile 1610 1615 1620	4964
gga ctc tat gga aat gga gta gtt acc aaa tca ggt gat tac gtc agt Gly Leu Tyr Gly Asn Gly Val Val Thr Lys Ser Gly Asp Tyr Val Ser 1625 1630 1635	5012
gcc ata acg caa gcc gaa aga att gga gag cca gat tat gaa gtg gat Ala Ile Thr Gln Ala Glu Arg Ile Gly Glu Pro Asp Tyr Glu Val Asp 1640 1645 1650	5060
gag gac att ttt cga aag aaa aga tta act ata atg gac tta cac ccc Glu Asp Ile Phe Arg Lys Lys Arg Leu Thr Ile Met Asp Leu His Pro 1655 1660 1665	5108
gga gct gga aag aca aaa aga att ctt cca tca ata gtg aga gaa gcc Gly Ala Gly Lys Thr Lys Arg Ile Leu Pro Ser Ile Val Arg Glu Ala 1670 1675 1680 1685	5156
tta aaa agg agg ctg cga acc ttg att ttg gct ccc acg aga gtg gtg Leu Lys Arg Arg Leu Arg Thr Leu Ile Leu Ala Pro Thr Arg Val Val 1690 1695 1700	5204
gcg gcc gag atg gaa gag gcc cta cgt gga ctg cca atc cgt tat cag Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu Pro Ile Arg Tyr Gln 1705 1710 1715	5252
acc cca gct gtg aaa tca gaa cac aca gga aga gag att gta gac ctc Thr Pro Ala Val Lys Ser Glu His Thr Gly Arg Glu Ile Val Asp Leu 1720 1725 1730	5300
atg tgt cat gca acc ttc aca aca aga ctt ttg tca tca acc aga gtt Met Cys His Ala Thr Phe Thr Thr Arg Leu Leu Ser Ser Thr Arg Val 1735 1740 1745	5348
cca aat tac aac ctc ata gtg atg gat gaa gca cat ttc acc gat cct Pro Asn Tyr Asn Leu Ile Val Met Asp Glu Ala His Phe Thr Asp Pro 1750 1755 1760 1765	5396
tct agt gtc gcg gct aga gga tac atc tcg acc agg gtg gaa atg gga Ser Ser Val Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Glu Met Gly 1770 1775 1780	5444

277

gag gca gca gcc atc ttc atg acc gca acc cct ccc gga gcg aca gat Glu Ala Ala Ala Ile Phe Met Thr Ala Thr Pro Pro Gly Ala Thr Asp 1785 1790 1795	5492
ccc ttt ccc cag agc aac agc cca ata gaa gac atc gag agg gaa att Pro Phe Pro Gln Ser Asn Ser Pro Ile Glu Asp Ile Glu Arg Glu Ile 1800 1805 1810	5540
ccg gaa agg tca tgg aac aca ggg ttc gac tgg ata aca gac tac caa Pro Glu Arg Ser Trp Asn Thr Gly Phe Asp Trp Ile Thr Asp Tyr Gln 1815 1820 1825	5588
ggg aaa act gtg tgg ttt gtt ccc agc ata aaa gct gga aat gac att Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile 1830 1835 1840 1845	5636
gca aat tgt ttg aga aag tgc gga aag aaa gtt atc cag ttg agt agg Ala Asn Cys Leu Arg Lys Ser Gly Lys Lys Val Ile Gln Leu Ser Arg 1850 1855 1860	5684
aaa acc ttt gat aca gag tat cca aaa acg aaa ctc acg gac tgg gat Lys Thr Phe Asp Thr Glu Tyr Pro Lys Thr Lys Leu Thr Asp Trp Asp 1865 1870 1875	5732
ttt gtg gtc act aca gac ata tct gaa atg ggg gcc aat ttt aga gct Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Arg Ala 1880 1885 1890	5780
ggg aga gtg ata gac cct agg aga tgc ctc aag cca gtt atc cta aca Gly Arg Val Ile Asp Pro Arg Arg Cys Leu Lys Pro Val Ile Leu Thr 1895 1900 1905	5828
gat ggg cca gag aga gtc att tta gca ggt cct att cca gtg act cca Asp Gly Pro Glu Arg Val Ile Leu Ala Gly Pro Ile Pro Val Thr Pro 1910 1915 1920 1925	5876
gca agc gct gct cag aga aga ggg cga ata gga agg aac cca gca caa Ala Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro Ala Gln 1930 1935 1940	5924
gaa gac gac caa tac gtt ttc tcc gga gac cca cta aaa aat gat gaa Glu Asp Asp Gln Tyr Val Phe Ser Gly Asp Pro Leu Lys Asn Asp Glu 1945 1950 1955	5972
gat cat gcc cac tgg aca gaa gca aag atg ctg ctt gac aat atc tac Asp His Ala His Trp Thr Glu Ala Lys Met Leu Leu Asp Asn Ile Tyr 1960 1965 1970	6020
acc cca gaa ggg atc att cca aca ttg ttt ggt ccg gaa agg gaa aaa Thr Pro Glu Gly Ile Ile Pro Thr Leu Phe Gly Pro Glu Arg Glu Lys 1975 1980 1985	6068
acc caa gcc att gat gga gag ttt cgc ctc aga ggg gaa caa agg aag Thr Gln Ala Ile Asp Gly Glu Phe Arg Leu Arg Gly Glu Gln Arg Lys 1990 1995 2000 2005	6116

278

act ttt gtg gaa tta atg agg aga gga gac ctt ccg gtg tgg ctg agc Thr Phe Val Glu Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ser 2010 2015 2020	6164
tat aag gta gct tct gct ggc att tct tac aaa gat cgg gaa tgg tgc Tyr Lys Val Ala Ser Ala Gly Ile Ser Tyr Lys Asp Arg Glu Trp Cys 2025 2030 2035	6212
ttc aca ggg gaa agg aat aac caa att tta gaa gaa aac atg gag gtt Phe Thr Gly Glu Arg Asn Asn Gln Ile Leu Glu Glu Asn Met Glu Val 2040 2045 2050	6260
gaa att tgg act aga gag gga gaa aag aaa aag cta agg cca aga tgg Glu Ile Trp Thr Arg Glu Gly Glu Lys Lys Lys Leu Arg Pro Arg Trp 2055 2060 2065	6308
tta gat gca cgt gta tac gct gac ccc atg gct ttg aag gat ttt aag Leu Asp Ala Arg Val Tyr Ala Asp Pro Met Ala Leu Lys Asp Phe Lys 2070 2075 2080 2085	6356
gag ttt gct agt gga agg aag agc ata act ctc gac atc cta aca gag Glu Phe Ala Ser Gly Arg Lys Ser Ile Thr Leu Asp Ile Leu Thr Glu 2090 2095 2100	6404
att gcc agt ttg cca act tac ctt tcc tct agg gcc aag ctc gcc ctt Ile Ala Ser Leu Pro Thr Tyr Leu Ser Arg Ala Lys Leu Ala Leu 2105 2110 2115	6452
gat aac ata gtc atg ctc cac aca aca gaa aga gga ggg agg gcc tac Asp Asn Ile Val Met Leu His Thr Thr Glu Arg Gly Gly Arg Ala Tyr 2120 2125 2130	6500
caa cac gcc ctg aac gaa ctc ccg gag tca ctg gaa aca ctt atg ctt Gln His Ala Leu Asn Glu Leu Pro Glu Ser Leu Glu Thr Leu Met Leu 2135 2140 2145	6548
gta gct tta cta ggt gct atg aca gca ggt atc ttc ctg ttt ttc atg Val Ala Leu Leu Gly Ala Met Thr Ala Gly Ile Phe Leu Phe Phe Met 2150 2155 2160 2165	6596
caa ggg aaa gga ata ggg aaa ttg tca atg ggt ttg ata acc att gcg Gln Gly Lys Gly Ile Gly Lys Leu Ser Met Gly Leu Ile Thr Ile Ala 2170 2175 2180	6644
gtg gct agt ggc ttg ctc tgg gta gca gaa att caa ccc cag tgg ata Val Ala Ser Gly Leu Leu Trp Val Ala Glu Ile Gln Pro Gln Trp Ile 2185 2190 2195	6692
gcg gcc tca atc ata cta gag ttt ttt ctc atg gta ctg ttg ata ccg Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Met Val Leu Leu Ile Pro 2200 2205 2210	6740

279

gaa cca gaa aaa caa agg acc cca caa gac aat caa ttg atc tac gtc Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn Gln Leu Ile Tyr Val 2215 2220 2225	6788
ata ttg acc att ctc acc att att ggt ctc ata gca gcc aac gag atg Ile Leu Thr Ile Leu Thr Ile Ile Gly Leu Ile Ala Ala Asn Glu Met 2230 2235 2240 2245	6836
ggg ctg att gaa aaa aca aaa acg gat ttt ggg ttt tac cag gta aaa Gly Leu Ile Glu Lys Thr Lys Thr Asp Phe Gly Phe Tyr Gln Val Lys 2250 2255 2260	6884
aca gaa acc acc atc ctc gat gtg gac ttg aga cca gct tca gca tgg Thr Glu Thr Thr Ile Leu Asp Val Asp Leu Arg Pro Ala Ser Ala Trp 2265 2270 2275	6932
acg ctc tat gca gta gcc acc aca att ctg act ccc atg ctg aga cac Thr Leu Tyr Ala Val Ala Thr Thr Ile Leu Thr Pro Met Leu Arg His 2280 2285 2290	6980
acc ata gaa aac acg tcg gcc aac cta tct cta gca gcc att gcc aac Thr Ile Glu Asn Thr Ser Ala Asn Leu Ser Leu Ala Ala Ile Ala Asn 2295 2300 2305	7028
cag gcg gcc gtc cta atg ggg ctt gga aaa gga tgg cgg ctc cac aga Gln Ala Ala Val Leu Met Gly Leu Gly Lys Gly Trp Pro Leu His Arg 2310 2315 2320 2325	7076
atg gac ctc ggt gtg ccg ctg tta gca atg gga tgc tat tct caa gtg Met Asp Leu Gly Val Pro Leu Leu Ala Met Gly Cys Tyr Ser Gln Val 2330 2335 2340	7124
aac cca aca act ttg aca gca tcc tta gtc atg ctt tta gtc cat tat Asn Pro Thr Thr Leu Thr Ala Ser Leu Val Met Leu Leu Val His Tyr 2345 2350 2355	7172
gca ata ata ggt cca gga ttg cag gca aaa gcc aca aga gag gcc cag Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg Glu Ala Gln 2360 2365 2370	7220
aaa agg aca gct gct ggg atc atg aaa aac ccc acg gtg gac ggg ata Lys Arg Thr Ala Ala Gly Ile Met Lys Asn Pro Thr Val Asp Gly Ile 2375 2380 2385	7268
aca gta ata gat cta gaa cca ata tcc tat gac cca aaa ttt gaa aag Thr Val Ile Asp Leu Glu Pro Ile Ser Tyr Asp Pro Lys Phe Glu Lys 2390 2395 2400 2405	7316
caa tta ggg cag gtc atg cta ctc gtc ttg tgt gct gga caa cta ctc Gln Leu Gly Gln Val Met Leu Leu Val Leu Cys Ala Gly Gln Leu Leu 2410 2415 2420	7364
ttg atg aga aca aca tgg gct ttc tgt gaa gtc ttg act ttg gcc aca Leu Met Arg Thr Thr Trp Ala Phe Cys Glu Val Leu Thr Leu Ala Thr 2425 2430 2435	7412

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gga cca atc ttg acc ttg tgg gag ggc aac ccg gga agg ttt tgg aac Gly Pro Ile Leu Thr Leu Trp Glu Gly Asn Pro Gly Arg Phe Trp Asn 2440 2445 2450	7460
acg acc ata gcc gta tcc acc gcc aac att ttc agg gga agt tac ctg Thr Thr Ile Ala Val Ser Thr Ala Asn Ile Phe Arg Gly Ser Tyr Leu 2455 2460 2465	7508
gcg gga gct gga ctg gct ttt tca ctc ata aag aat gca caa acc cct Ala Gly Ala Gly Leu Ala Phe Ser Leu Ile Lys Asn Ala Gln Thr Pro 2470 2475 2480 2485	7556
agg agg gga act ggg acc aca gga gag aca ctg gga gag aag tgg aag Arg Arg Gly Thr Gly Thr Thr Gly Glu Thr Leu Gly Glu Lys Trp Lys 2490 2495 2500	7604
aga cag cta aac tca tta gac aga aaa gag ttt gaa gag tat aaa aga Arg Gln Leu Asn Ser Leu Asp Arg Lys Glu Phe Glu Glu Tyr Lys Arg 2505 2510 2515	7652
agt gga ata cta gaa gtg gac agg act gaa gcc aag tct gcc ctg aaa Ser Gly Ile Leu Glu Val Asp Arg Thr Glu Ala Lys Ser Ala Leu Lys 2520 2525 2530	7700
gat ggg tct aaa atc aag cat gca gta tct aga ggg tcc agt aag att Asp Gly Ser Lys Ile Lys His Ala Val Ser Arg Gly Ser Ser Lys Ile 2535 2540 2545	7748
aga tgg att gtt gag aga ggg atg gta aag cca aaa ggg aaa gtt gta Arg Trp Ile Val Glu Arg Gly Met Val Lys Pro Lys Gly Lys Val Val 2550 2555 2560 2565	7796
gat ctt ggc tgt ggg aga gga gga tgg tct tat tac atg gcg acg ctc Asp Leu Gly Cys Gly Arg Gly Gly Trp Ser Tyr Tyr Met Ala Thr Leu 2570 2575 2580	7844
aag aac gtg act gaa gtg aaa ggg tat aca aaa gga ggt cca gga cat Lys Asn Val Thr Glu Val Lys Gly Tyr Thr Lys Gly Gly Pro Gly His 2585 2590 2595	7892
gaa gaa ccg att ccc atg gct act tat ggc tgg aat ttg gtc aaa ctc Glu Glu Pro Ile Pro Met Ala Thr Tyr Gly Trp Asn Leu Val Lys Leu 2600 2605 2610	7940
cat tca ggg gtt gac gtg ttc tac aaa ccc aca gag caa gtg gac acc His Ser Gly Val Asp Val Phe Tyr Lys Pro Thr Glu Gln Val Asp Thr 2615 2620 2625	7988
ctg ctc tgt gat att ggg gag tca tct tct aat cca aca ata gag gaa Leu Leu Cys Asp Ile Gly Glu Ser Ser Ser Asn Pro Thr Ile Glu Glu 2630 2635 2640 2645	8036

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gga aga aca tta aga gtt ttg aag atg gtg gag cca tgg ctc tct tca	8084
Gly Arg Thr Leu Arg Val Leu Lys Met Val Glu Pro Trp Leu Ser Ser	
2650 2655 2660	
aaa cct gaa ttc tgc atc aaa gtc ctt aac ccc tac atg cca aca gtc	8132
Lys Pro Glu Phe Cys Ile Lys Val Leu Asn Pro Tyr Met Pro Thr Val	
2665 2670 2675	
ata gaa gag ctg gag aaa ctg cag aga aaa cat ggt ggg aac ctt gtc	8180
Ile Glu Glu Leu Glu Lys Leu Gln Arg Lys His Gly Gly Asn Leu Val	
2680 2685 2690	
aga tgc ccg ctg tcc agg aac tcc acc cat gag atg tat tgg gtg tca	8228
Arg Cys Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr Trp Val Ser	
2695 2700 2705	
gga gcg tcg gga aac att gtg agc tct gtg aac aca aca tca aag atg	8276
Gly Ala Ser Gly Asn Ile Val Ser Ser Val Asn Thr Thr Ser Lys Met	
2710 2715 2720 2725	
ttg ttg aac agg ttc aca aca agg cat agg aaa ccc act tat gag aag	8324
Leu Leu Asn Arg Phe Thr Thr Arg His Arg Lys Pro Thr Tyr Glu Lys	
2730 2735 2740	
gac gta gat ctt ggg gca gga acg aga agt gtc tcc act gaa aca gaa	8372
Asp Val Asp Leu Gly Ala Gly Thr Arg Ser Val Ser Thr Glu Thr Glu	
2745 2750 2755	
aaa cca gac atg aca att att ggg aga agg ctt cag cga ttg caa gag	8420
Lys Pro Asp Met Thr Ile Ile Gly Arg Arg Leu Gln Arg Leu Gln Glu	
2760 2765 2770	
gag cac aaa gaa acc tgg cat tat gat cag gaa aac cca tac aga acc	8468
Glu His Lys Glu Thr Trp His Tyr Asp Gln Glu Asn Pro Tyr Arg Thr	
2775 2780 2785	
tgg gcg tat cat gga agc tat gaa gct cct tcg aca ggc tct gca tcc	8516
Trp Ala Tyr His Gly Ser Tyr Glu Ala Pro Ser Thr Gly Ser Ala Ser	
2790 2795 2800 2805	
tcc atg gtg aac ggg gta gta aaa ctg cta aca aaa cct tgg gat gtg	8564
Ser Met Val Asn Gly Val Val Lys Leu Leu Thr Lys Pro Trp Asp Val	
2810 2815 2820	
gtt cca atg gtg acc cag tta gcc atg aca gac aca acc cct ttt ggg	8612
Val Pro Met Val Thr Gln Leu Ala Met Thr Asp Thr Thr Pro Phe Gly	
2825 2830 2835	
caa caa aga gtg ttc aaa gag aag gtg gat acc aga aca cca caa cca	8660
Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr Pro Gln Pro	
2840 2845 2850	
aaa ccc ggt aca cga atg gtt atg acc acg aca gcc aat tgg ctg tgg	8708
Lys Pro Gly Thr Arg Met Val Met Thr Thr Thr Ala Asn Trp Leu Trp	
2855 2860 2865	

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gcc ctc ctt ggg aag aag aaa aat ccc aga ctg tgc aca agg gaa gag Ala Leu Leu Gly Lys Lys Lys Asn Pro Arg Leu Cys Thr Arg Glu Glu 2870 2875 2880 2885	8756
ttc atc tca aaa gtt aga tca aac gca gcc ata ggc gca gtc ttt cag Phe Ile Ser Lys Val Arg Ser Asn Ala Ala Ile Gly Ala Val Phe Gln 2890 2895 2900	8804
gaa gaa cag gga tgg aca tca gcc agt gaa gct gtg aat gac agc cgg Glu Glu Gln Gly Trp Thr Ser Ala Ser Glu Ala Val Asn Asp Ser Arg 2905 2910 2915	8852
ttt tgg gaa ctg gtt gac aaa gaa agg gcc cta cac cag gaa ggg aaa Phe Trp Glu Leu Val Asp Lys Glu Arg Ala Leu His Gln Glu Gly Lys 2920 2925 2930	8900
tgt gaa tcg tgt gtc tac aac atg atg gga aaa cgt gag aaa aag tta Cys Glu Ser Cys Val Tyr Asn Met Met Gly Lys Arg Glu Lys Lys Leu 2935 2940 2945	8948
gga gag ttt ggc aga gcc aag gga agc cga gca atc tgg tac atg tgg Gly Glu Phe Gly Arg Ala Lys Gly Ser Arg Ala Ile Trp Tyr Met Trp 2950 2955 2960 2965	8996
ctg gga gcg cgg ttt ctg gaa ttt gaa gcc ctg ggt ttt ttg aat gaa Leu Gly Ala Arg Phe Leu Glu Phe Glu Ala Leu Gly Phe Leu Asn Glu 2970 2975 2980	9044
gat cac tgg ttt ggc aga gaa aat tca tgg agt gga gtg gaa ggg gaa Asp His Trp Phe Gly Arg Glu Asn Ser Trp Ser Gly Val Glu Gly Glu 2985 2990 2995	9092
ggt ctg cac aga ttg gga tat atc ctg gag gag ata gac aag aag gat Gly Leu His Arg Leu Gly Tyr Ile Leu Glu Glu Ile Asp Lys Lys Asp 3000 3005 3010	9140
gga gac cta atg tat gct gat gac aca gca ggc tgg gac aca aga atc Gly Asp Leu Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp Thr Arg Ile 3015 3020 3025	9188
act gag gat gac ctt caa aat gaa gaa ctg atc acg gaa cag atg gcc Thr Glu Asp Asp Leu Gln Asn Glu Glu Leu Ile Thr Glu Gln Met Ala 3030 3035 3040 3045	9236
ccc cac cac aag atc cta gcc aaa gcc att ttc aaa cta acc tat caa Pro His His Lys Ile Leu Ala Lys Ala Ile Phe Lys Leu Thr Tyr Gln 3050 3055 3060	9284
aac aaa gtg gtg aaa gtc ctc aga ccc aca cgg aga gga gcg gtg atg Asn Lys Val Val Lys Val Leu Arg Pro Thr Pro Arg Gly Ala Val Met 3065 3070 3075	9332

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gat atc ata tcc agg aaa gac caa aga ggt agt gga caa gtt gga aca Asp Ile Ile Ser Arg Lys Asp Gln Arg Gly Ser Gly Gln Val Gly Thr 3080 3085 3090	9380
tat ggt ttg aac aca ttc acc aac atg gaa gtt caa ctc atc cgc caa Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Val Gln Leu Ile Arg Gln 3095 3100 3105	9428
atg gaa gct gaa gga gtc atc aca caa gat gac atg cag aac cca aaa Met Glu Ala Glu Gly Val Ile Thr Gln Asp Asp Met Gln Asn Pro Lys 3110 3115 3120 3125	9476
ggg ttg aaa gaa aga gtt gag aaa tgg ctg aaa gag tgt ggt gtc gac Gly Leu Lys Glu Arg Val Glu Lys Trp Leu Lys Glu Cys Gly Val Asp 3130 3135 3140	9524
agg tta aag agg atg gca atc agt gga gac gat tgc gtg gtg aag ccc Arg Leu Lys Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val Lys Pro 3145 3150 3155	9572
ctg gat gag agg ttt ggc act tcc ctc ctc ttc ttg aac gac atg gga Leu Asp Glu Arg Phe Gly Thr Ser Leu Leu Phe Leu Asn Asp Met Gly 3160 3165 3170	9620
aag gtg agg aaa gac att ccg cag tgg gaa cca tct aag gga tgg aaa Lys Val Arg Lys Asp Ile Pro Gln Trp Glu Pro Ser Lys Gly Trp Lys 3175 3180 3185	9668
aac tgg caa gag gtt cct ttt tgc tcc cac cac ttt cac aag atc ttc Asn Trp Gln Glu Val Pro Phe Cys Ser His His Phe His Lys Ile Phe 3190 3195 3200 3205	9716
atg aag gat ggc cgc tca cta gtt gtt cca tgt aga aac cag gat gaa Met Lys Asp Gly Arg Ser Leu Val Val Pro Cys Arg Asn Gln Asp Glu 3210 3215 3220	9764
ctg ata ggg aga gcc aga atc tgc cag ggg gct gga tgg agc tta aga Leu Ile Gly Arg Ala Arg Ile Ser Gln Gly Ala Gly Trp Ser Leu Arg 3225 3230 3235	9812
gaa aca gcc tgc ctg ggc aaa gct tac gcc cag atg tgg tgc ctc atg Glu Thr Ala Cys Leu Gly Lys Ala Tyr Ala Gln Met Trp Ser Leu Met 3240 3245 3250	9860
tac ttc cac aga agg gat ctg cgt tta gcc tcc atg gcc ata tgc tca Tyr Phe His Arg Arg Asp Leu Arg Leu Ala Ser Met Ala Ile Cys Ser 3255 3260 3265	9908
gca gtt cca acg gaa tgg ttt cca aca agc aga aca aca tgg tca atc Ala Val Pro Thr Glu Trp Phe Pro Thr Ser Arg Thr Thr Trp Ser Ile 3270 3275 3280 3285	9956
cac gct cat cat cag tgg atg acc act gaa gat atg ctc aaa gtg tgg His Ala His His Gln Trp Met Thr Thr Glu Asp Met Leu Lys Val Trp 3290 3295 3300	10004

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aac aga gtg tgg ata gaa gac aac cct aat atg act gac aag act cca 10052
 Asn Arg Val Trp Ile Glu Asp Asn Pro Asn Met Thr Asp Lys Thr Pro
 3305 3310 3315

gtc cat tcg tgg gaa gat ata cct tac cta ggg aaa aga gag gat ttg 10100
 Val His Ser Trp Glu Asp Ile Pro Tyr Leu Gly Lys Arg Glu Asp Leu
 3320 3325 3330

tgg tgt gga tcc ctg att gga ctt tct tcc aga gcc acc tgg gcg aag 10148
 Trp Cys Gly Ser Leu Ile Gly Leu Ser Ser Arg Ala Thr Trp Ala Lys
 3335 3340 3345

aac att cac acg gcc ata acc cag gtc aga aac ctg atc gga aaa gag 10196
 Asn Ile His Thr Ala Ile Thr Gln Val Arg Asn Leu Ile Gly Lys Glu
 3350 3355 3360 3365

gaa tac gtg gat tac atg cca gta atg aaa aga tac agc gct cct tca 10244
 Glu Tyr Val Asp Trp Met Pro Val Met Lys Arg Tyr Ser Ala Pro Ser
 3370 3375 3380

gag agt gaa gga gtt ctg taa ttaccaacaa caaacaccaa aggctattga 10295
 Glu Ser Glu Gly Val Leu *
 3385

agtcaggcca cttgtgccac ggcttgagca aaccgtgctg cctgtagctc cgccaataat 10355
 gggaggcgctg aaatccctag ggaggccatg cgccacggaa gctgtacgctg tggcatattg 10415
 gactagcggg tagaggagac ccctcccatc actgacaaaa cgcagcaaaa gggggcccgga 10475
 agccaggagg aagctgtact cctggtggaa ggactagagg ttagaggaga ccccccaac 10535
 acaaaaacag catattgacg ctgggaaga cagagatcc tgctgtctct gcaacatcaa 10595
 tccaggcaca gagcgaagca agatggattg gtgtgttga tccaacaggt tct 10648

<210> 24

<211> 3387

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
 synthetic construct

<400> 24

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 Arg Glu Arg Asn Arg Val Ser Thr Pro Gln Gly Leu Val Lys Arg Phe
 20 25 30
 Ser Thr Gly Leu Phe Ser Gly Lys Gly Pro Leu Arg Met Val Leu Ala
 35 40 45
 Phe Ile Thr Phe Leu Arg Val Leu Ser Ile Pro Pro Thr Ala Gly Ile
 50 55 60
 Leu Lys Arg Trp Gly Gln Leu Lys Lys Asn Lys Ala Ile Arg Ile Leu
 65 70 75 80
 Ile Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn Gly
 85 90 95

Arg	Lys	Arg	Ser	Thr	Ile	Thr	Leu	Leu	Cys	Leu	Ile	Pro	Thr	Val	Met
Ala	Phe	His	Leu	Ser	Thr	Arg	Asp	Gly	Glu	Pro	Leu	Met	Ile	Val	Ala
Lys	His	Glu	Arg	Gly	Arg	Pro	Leu	Leu	Phe	Lys	Thr	Thr	Glu	Gly	Ile
Asn	Lys	Cys	Thr	Leu	Ile	Ala	Met	Asp	Leu	Gly	Glu	Met	Cys	Glu	Asp
Thr	Val	Thr	Tyr	Lys	Cys	Pro	Leu	Leu	Val	Asn	Thr	Glu	Pro	Glu	Asp
Ile	Asp	Cys	Trp	Cys	Asn	Leu	Thr	Ser	Thr	Trp	Val	Met	Tyr	Gly	Thr
Cys	Thr	Gln	Ser	Gly	Glu	Arg	Arg	Glu	Lys	Arg	Ser	Val	Ala	Leu	
Thr	Pro	His	Ser	Gly	Met	Gly	Leu	Glu	Thr	Arg	Ala	Glu	Thr	Trp	Met
Ser	Ser	Glu	Gly	Ala	Trp	Lys	His	Ala	Gln	Arg	Val	Glu	Ser	Trp	Ile
Leu	Arg	Asn	Pro	Gly	Phe	Ala	Leu	Leu	Ala	Gly	Phe	Met	Ala	Tyr	Met
Ile	Gly	Gln	Thr	Gly	Ile	Gln	Arg	Thr	Val	Phe	Phe	Val	Leu	Met	Met
Leu	Val	Ala	Pro	Ser	Tyr	Gly	Met	Arg	Cys	Val	Gly	Val	Gly	Asn	Arg
Asp	Phe	Val	Glu	Gly	Val	Ser	Gly	Gly	Ala	Trp	Val	Asp	Leu	Val	Leu
Glu	His	Gly	Gly	Cys	Val	Thr	Thr	Met	Ala	Gln	Gly	Lys	Pro	Thr	Leu
Asp	Phe	Glu	Leu	Thr	Lys	Thr	Thr	Ala	Lys	Glu	Val	Ala	Leu	Leu	Arg
Thr	Tyr	Cys	Ile	Glu	Ala	Ser	Ile	Ser	Asn	Ile	Thr	Thr	Ala	Thr	Arg
Cys	Pro	Thr	Gln	Gly	Glu	Pro	Tyr	Leu	Lys	Glu	Glu	Gln	Asp	Gln	Gln
Tyr	Ile	Cys	Arg	Arg	Asp	Val	Val	Asp	Arg	Gly	Trp	Gly	Asn	Gly	Cys
Gly	Leu	Phe	Gly	Lys	Gly	Gly	Val	Val	Thr	Cys	Ala	Lys	Phe	Ser	Cys
Ser	Gly	Lys	Ile	Thr	Gly	Asn	Leu	Val	Gln	Ile	Glu	Asn	Leu	Glu	Tyr
Thr	Val	Val	Val	Thr	Val	His	Asn	Gly	Asp	Thr	His	Ala	Val	Gly	Asn
Asp	Thr	Ser	Asn	His	Gly	Val	Thr	Ala	Thr	Ile	Thr	Pro	Arg	Ser	Pro
Ser	Val	Glu	Val	Lys	Leu	Pro	Asp	Tyr	Gly	Glu	Leu	Thr	Leu	Asp	Cys
Glu	Pro	Arg	Ser	Gly	Ile	Asp	Phe	Asn	Glu	Met	Ile	Leu	Met	Lys	Met
Lys	Lys	Lys	Thr	Trp	Leu	Val	His	Lys	Gln	Trp	Phe	Leu	Asp	Leu	Pro
Leu	Pro	Trp	Thr	Ala	Gly	Ala	Asp	Thr	Ser	Glu	Val	His	Trp	Asn	Tyr
Lys	Glu	Arg	Met	Val	Thr	Phe	Lys	Val	Pro	His	Ala	Lys	Arg	Gln	Asp

Val	Thr	Val	Leu	Gly	Ser	Gln	Glu	Gly	Ala	Met	His	Ser	Ala	Leu	Ala
530						535					540				
Gly	Ala	Thr	Glu	Val	Asp	Ser	Gly	Asp	Gly	Asn	His	Met	Phe	Ala	Gly
545					550					555					560
His	Leu	Lys	Cys	Lys	Val	Arg	Met	Glu	Lys	Leu	Arg	Ile	Lys	Gly	Met
				565						570					575
Ser	Tyr	Thr	Met	Cys	Ser	Gly	Lys	Phe	Ser	Ile	Asp	Lys	Glu	Met	Ala
			580						585						590
Glu	Thr	Gln	His	Gly	Thr	Thr	Val	Val	Lys	Val	Lys	Tyr	Glu	Gly	Ala
							600					605			
Gly	Ala	Pro	Cys	Lys	Val	Pro	Ile	Glu	Ile	Arg	Asp	Val	Asn	Lys	Glu
						615						620			
Lys	Val	Val	Gly	Arg	Ile	Ile	Ser	Ser	Thr	Pro	Leu	Ala	Glu	Asn	Thr
625					630					635					640
Asn	Ser	Ala	Thr	Asn	Ile	Glu	Leu	Glu	Pro	Pro	Phe	Gly	Asp	Ser	Tyr
				645						650					655
Ile	Val	Ile	Gly	Val	Gly	Asn	Ser	Ala	Leu	Thr	Leu	His	Trp	Phe	Arg
				660						665					670
Lys	Gly	Ser	Ser	Ile	Gly	Lys	Met	Phe	Glu	Ser	Thr	Tyr	Arg	Gly	Ala
							680					685			
Lys	Arg	Met	Ala	Ile	Leu	Gly	Glu	Thr	Ala	Trp	Asp	Phe	Gly	Ser	Val
						695					700				
Gly	Gly	Leu	Phe	Thr	Ser	Leu	Gly	Lys	Ala	Val	His	Gln	Val	Phe	Gly
705					710					715					720
Ser	Val	Tyr	Thr	Thr	Met	Phe	Gly	Gly	Val	Ser	Trp	Met	Ile	Arg	Ile
				725						730					735
Leu	Ile	Gly	Phe	Leu	Val	Leu	Trp	Ile	Gly	Thr	Asn	Ser	Arg	Asn	Thr
				740						745					750
Ser	Met	Ala	Met	Thr	Cys	Ile	Ala	Val	Gly	Gly	Ile	Thr	Leu	Phe	Leu
				755				760				765			
Gly	Phe	Thr	Val	Gln	Ala	Asp	Met	Gly	Cys	Val	Val	Ser	Trp	Ser	Gly
						775					780				
Lys	Glu	Leu	Lys	Cys	Gly	Ser	Gly	Ile	Phe	Val	Val	Asp	Asn	Val	His
785					790					795					800
Thr	Trp	Thr	Glu	Gln	Tyr	Lys	Phe	Gln	Pro	Glu	Ser	Pro	Ala	Arg	Leu
				805						810					815
Ala	Ser	Ala	Ile	Leu	Asn	Ala	His	Lys	Asp	Gly	Val	Cys	Gly	Ile	Arg
				820					825						830
Ser	Thr	Thr	Arg	Leu	Glu	Asn	Val	Met	Trp	Lys	Gln	Ile	Thr	Asn	Glu
				835					840						845
Leu	Asn	Tyr	Val	Leu	Trp	Glu	Gly	Gly	His	Asp	Leu	Thr	Val	Val	Ala
						855					860				
Gly	Asp	Val	Lys	Gly	Val	Leu	Thr	Lys	Gly	Lys	Arg	Ala	Leu	Thr	Pro
865					870					875					880
Pro	Val	Asn	Asp	Leu	Lys	Tyr	Ser	Trp							

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Ala Ile Lys Asp Gln Lys Ala Val His Ala Asp Met Gly Tyr Trp Ile
 965 970 975
 Glu Ser Ser Lys Asn Gln Thr Trp Gln Ile Glu Lys Ala Ser Leu Ile
 980 985 990
 Glu Val Lys Thr Cys Leu Trp Pro Lys Thr His Thr Leu Trp Ser Asn
 995 1000 1005
 Gly Val Leu Glu Ser Gln Met Leu Ile Pro Lys Ser Tyr Ala Gly Pro
 1010 1015 1020
 Phe Ser Gln His Asn Tyr Arg Gln Gly Tyr Ala Thr Gln Thr Val Gly
 1025 1030 1035 1040
 Pro Trp His Leu Gly Lys Leu Glu Ile Asp Phe Gly Glu Cys Pro Gly
 1045 1050 1055
 Thr Thr Val Ala Ile Gln Glu Asp Cys Asp His Arg Gly Pro Ser Leu
 1060 1065 1070
 Arg Thr Thr Thr Ala Ser Gly Lys Leu Val Thr Gln Trp Cys Cys Arg
 1075 1080 1085
 Ser Cys Thr Met Pro Pro Leu Arg Phe Leu Gly Glu Asp Gly Cys Trp
 1090 1095 1100
 Tyr Gly Met Glu Ile Arg Pro Leu Ser Glu Lys Glu Glu Asn Met Val
 1105 1110 1115 1120
 Lys Ser Gln Val Thr Ala Gly Gln Gly Thr Ser Glu Thr Phe Ser Met
 1125 1130 1135
 Gly Leu Leu Cys Leu Thr Leu Phe Val Glu Glu Cys Leu Arg Arg Arg
 1140 1145 1150
 Val Thr Arg Lys His Met Ile Leu Val Val Val Ile Thr Leu Cys Ala
 1155 1160 1165
 Ile Ile Leu Gly Gly Leu Thr Trp Met Asp Leu Leu Arg Ala Leu Ile
 1170 1175 1180
 Met Leu Gly Asp Thr Met Ser Gly Arg Ile Gly Gly Gln Ile His Leu
 1185 1190 1195 1200
 Ala Ile Met Ala Val Phe Lys Met Ser Pro Gly Tyr Val Leu Gly Val
 1205 1210 1215
 Phe Leu Arg Lys Leu Thr Ser Arg Glu Thr Ala Leu Met Val Ile Gly
 1220 1225 1230
 Met Ala Met Thr Thr Val Leu Ser Ile Pro His Asp Leu Met Glu Leu
 1235 1240 1245
 Ile Asp Gly Ile Ser Leu Gly Leu Ile Leu Leu Lys Ile Val Thr His
 1250 1255 1260
 Phe Asp Asn Thr Gln Val Gly Thr Leu Ala Leu Ser Leu Thr Phe Ile
 1265 1270 1275 1280
 Arg Ser Thr Met Pro Leu Val Met Ala Trp Arg Thr Ile Met Ala Val
 1285 1290 1295
 Leu Phe Val Val Thr Leu Ile Pro Leu Cys Arg Thr Ser Cys Leu Gln
 1300 1305 1310
 Lys Gln Ser His Trp Val Glu Ile Thr Ala Leu Ile Leu Gly Ala Gln
 1315 1320 1325
 Ala Leu Pro Val Tyr Leu Met Thr Leu Met Lys Gly Ala Ser Arg Arg
 1330 1335 1340
 Ser Trp Pro Leu Asn Glu Gly Ile Met Ala Val Gly Leu Val Ser Leu
 1345 1350 1355 1360
 Leu Gly Ser Ala Leu Leu Lys Asn Asp Val Pro Leu Ala Gly Pro Met
 1365 1370 1375
 Val Ala Gly Gly Leu Leu Leu Ala Ala Tyr Val Met Ser Gly Ser Ser
 1380 1385 1390

288

Ala Asp Leu Ser Leu Glu Lys Ala Ala Asn Val Gln Trp Asp Glu Met
 1395 1400 1405
 Ala Asp Ile Thr Gly Ser Ser Pro Ile Ile Glu Val Lys Gln Asp Glu
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 Asp Gly Ser Phe Ser Ile Arg Asp Val Glu Glu Thr Asn Met Ile Thr
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 Leu Leu Val Lys Leu Ala Leu Ile Thr Val Ser Gly Leu Tyr Pro Leu
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 Gln Arg Ser Gly Ala Leu Trp Asp Val Pro Ser Pro Ala Ala Thr Gln
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 Lys Ala Ala Leu Ser Glu Gly Val Tyr Arg Ile Met Gln Arg Gly Leu
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 Phe Gly Lys Thr Gln Val Gly Val Gly Ile His Met Glu Gly Val Phe
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 His Thr Met Trp His Val Thr Arg Gly Ser Val Ile Cys His Glu Thr
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 Gly Arg Leu Glu Pro Ser Trp Ala Asp Val Arg Asn Asp Met Ile Ser
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 Tyr Gly Gly Gly Trp Arg Leu Gly Asp Lys Trp Asp Lys Glu Glu Asp
 1555 1560 1565
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 Thr Lys Pro Gly Leu Phe Lys Thr Leu Thr Gly Glu Ile Gly Ala Val
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 1650 1655 1660
 Met Asp Leu His Pro Gly Ala Gly Lys Thr Lys Arg Ile Leu Pro Ser
 1665 1670 1675 1680
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 1685 1690 1695
 Pro Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu
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 Pro Ile Arg Tyr Gln Thr Pro Ala Val Lys Ser Glu His Thr Gly Arg
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 Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Thr Arg Leu Leu
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 Ser Ser Thr Arg Val Pro Asn Tyr Asn Leu Ile Val Met Asp Glu Ala
 1745 1750 1755 1760
 His Phe Thr Asp Pro Ser Ser Val Ala Ala Arg Gly Tyr Ile Ser Thr
 1765 1770 1775
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 1780 1785 1790
 Pro Gly Ala Thr Asp Pro Phe Pro Gln Ser Asn Ser Pro Ile Glu Asp
 1795 1800 1805
 Ile Glu Arg Glu Ile Pro Glu Arg Ser Trp Asn Thr Gly Phe Asp Trp
 1810 1815 1820

Ile Thr Asp Tyr Gln Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys
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 Ala Gly Asn Asp Ile Ala Asn Cys Leu Arg Lys Ser Gly Lys Lys Val
 1845 1850 1855
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 1860 1865 1870
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 Ala Asn Phe Arg Ala Gly Arg Val Ile Asp Pro Arg Arg Cys Leu Lys
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 Pro Val Ile Leu Thr Asp Gly Pro Glu Arg Val Ile Leu Ala Gly Pro
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 Ile Pro Val Thr Pro Ala Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly
 1925 1930 1935
 Arg Asn Pro Ala Gln Glu Asp Asp Gln Tyr Val Phe Ser Gly Asp Pro
 1940 1945 1950
 Leu Lys Asn Asp Glu Asp His Ala His Trp Thr Glu Ala Lys Met Leu
 1955 1960 1965
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 Pro Glu Arg Glu Lys Thr Gln Ala Ile Asp Gly Glu Phe Arg Leu Arg
 1985 1990 1995 2000
 Gly Glu Gln Arg Lys Thr Phe Val Glu Leu Met Arg Arg Gly Asp Leu
 2005 2010 2015
 Pro Val Trp Leu Ser Tyr Lys Val Ala Ser Ala Gly Ile Ser Tyr Lys
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 Gln Pro Gln Trp Ile Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Met
 2195 2200 2205
 Val Leu Leu Ile Pro Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn
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 Gln Leu Ile Tyr Val Ile Leu Thr Ile Leu Thr Ile Ile Gly Leu Ile
 2225 2230 2235 2240
 Ala Ala Asn Glu Met Gly Leu Ile Glu Lys Thr Lys Thr Asp Phe Gly
 2245 2250 2255

290

Phe Tyr Gln Val Lys Thr Glu Thr Thr Ile Leu Asp Val Asp Leu Arg
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 Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Ile Leu Thr
 2275 2280 2285
 Pro Met Leu Arg His Thr Ile Glu Asn Thr Ser Ala Asn Leu Ser Leu
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 2580 2585 2590
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 2595 2600 2605
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 2610 2615 2620
 Glu Gln Val Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Ser Asn
 2625 2630 2635 2640
 Pro Thr Ile Glu Glu Gly Arg Thr Leu Arg Val Leu Lys Met Val Glu
 2645 2650 2655
 Pro Trp Leu Ser Ser Lys Pro Glu Phe Cys Ile Lys Val Leu Asn Pro
 2660 2665 2670
 Tyr Met Pro Thr Val Ile Glu Glu Leu Glu Lys Leu Gln Arg Lys His
 2675 2680 2685

291

Gly Gly Asn Leu Val Arg Cys Pro Leu Ser Arg Asn Ser Thr His Glu
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 Met Tyr Trp Val Ser Gly Ala Ser Gly Asn Ile Val Ser Ser Val Asn
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 Ser Thr Glu Thr Glu Lys Pro Asp Met Thr Ile Ile Gly Arg Arg Leu
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 3010 3015 3020
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 Thr Glu Gln Met Ala Pro His His Lys Ile Leu Ala Lys Ala Ile Phe
 3045 3050 3055
 Lys Leu Thr Tyr Gln Asn Lys Val Val Lys Val Leu Arg Pro Thr Pro
 3060 3065 3070
 Arg Gly Ala Val Met Asp Ile Ile Ser Arg Lys Asp Gln Arg Gly Ser
 3075 3080 3085
 Gly Gln Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Val
 3090 3095 3100
 Gln Leu Ile Arg Gln Met Glu Ala Glu Gly Val Ile Thr Gln Asp Asp
 3105 3110 3115 3120

292

Met Gln Asn Pro Lys Gly Leu Lys Glu Arg Val Glu Lys Trp Leu Lys
 3125 3130 3135
 Glu Cys Gly Val Asp Arg Leu Lys Arg Met Ala Ile Ser Gly Asp Asp
 3140 3145 3150
 Cys Val Val Lys Pro Leu Asp Glu Arg Phe Gly Thr Ser Leu Leu Phe
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 Ser Lys Gly Trp Lys Asn Trp Gln Glu Val Pro Phe Cys Ser His His
 3185 3190 3195 3200
 Phe His Lys Ile Phe Met Lys Asp Gly Arg Ser Leu Val Val Pro Cys
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 3235 3240 3245
 Met Trp Ser Leu Met Tyr Phe His Arg Arg Asp Leu Arg Leu Ala Ser
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 Met Ala Ile Cys Ser Ala Val Pro Thr Glu Trp Phe Pro Thr Ser Arg
 3265 3270 3275 3280
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 Thr Asp Lys Thr Pro Val His Ser Trp Glu Asp Ile Pro Tyr Leu Gly
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 Lys Arg Glu Asp Leu Trp Cys Gly Ser Leu Ile Gly Leu Ser Ser Arg
 3330 3335 3340
 Ala Thr Trp Ala Lys Asn Ile His Thr Ala Ile Thr Gln Val Arg Asn
 3345 3350 3355 3360
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<211> 10648

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<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
 synthetic construct

<221> CDS

<222> (102)...(10265)

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 ttctaacagt ttgtttgaat agagagcaga tctctggaaa a atg aac caa cga aaa 116
 Met Asn Gln Arg Lys
 1 5

293

aag gtg gtt aga cca cct ttc aat atg ctg aaa cgc gag aga aac cgc Lys Val Val Arg Pro Pro Phe Asn Met Leu Lys Arg Glu Arg Asn Arg	164
10 15 20	
gta tca acc cct caa ggg ttg gtg aag aga ttc tca acc gga ctt ttt Val Ser Thr Pro Gln Gly Leu Val Lys Arg Phe Ser Thr Gly Leu Phe	212
25 30 35	
tct ggg aaa gga ccc tta cgg atg gtg cta gca ttc atc acg ttt ttg Ser Gly Lys Gly Pro Leu Arg Met Val Leu Ala Phe Ile Thr Phe Leu	260
40 45 50	
cga gtc ctt tcc atc cca cca aca gca ggg att ctg aaa aga tgg gga Arg Val Leu Ser Ile Pro Pro Thr Ala Gly Ile Leu Lys Arg Trp Gly	308
55 60 65	
cag ttg aag aaa aat aag gcc atc agg ata ctg att gga ttc agg aag Gln Leu Lys Lys Asn Lys Ala Ile Arg Ile Leu Ile Gly Phe Arg Lys	356
70 75 80 85	
gag ata ggc cgc atg ctg aac atc ttg aac ggg aga aaa agg tca acg Glu Ile Gly Arg Met Leu Asn Ile Leu Asn Gly Arg Lys Arg Ser Thr	404
90 95 100	
ata aca ttg ctg tgc ttg att ccc acc gta atg gcg ttt cac ttg tca Ile Thr Leu Leu Cys Leu Ile Pro Thr Val Met Ala Phe His Leu Ser	452
105 110 115	
aca aga gat ggc gaa ccc ctc atg ata gtg gca aaa cat gaa agg ggg Thr Arg Asp Gly Glu Pro Leu Met Ile Val Ala Lys His Glu Arg Gly	500
120 125 130	
aga cct ctc ttg ttt aag aca aca gag ggg atc aac aaa tgc act ctc Arg Pro Leu Leu Phe Lys Thr Thr Glu Gly Ile Asn Lys Cys Thr Leu	548
135 140 145	
att gcc atg gac ttg ggt gaa atg tgt gag gac act gtc acg tat aaa Ile Ala Met Asp Leu Gly Glu Met Cys Glu Asp Thr Val Thr Tyr Lys	596
150 155 160 165	
tgc ccc tta ctg gtc aat acc gaa cct gaa gac att gat tgc tgg tgc Cys Pro Leu Leu Val Asn Thr Glu Pro Glu Asp Ile Asp Cys Trp Cys	644
170 175 180	
aat ctc acg tct acc tgg gtc atg tat ggg aca tgc acc cag agc gga Asn Leu Thr Ser Thr Trp Val Met Tyr Gly Thr Cys Thr Gln Ser Gly	692
185 190 195	
gaa cgg aga cga gag aag cgc tca gta gct tta aca cca cat tca gga Glu Arg Arg Arg Glu Lys Arg Ser Val Ala Leu Thr Pro His Ser Gly	740
200 205 210	
atg gga ttg gaa aca aga gct gag aca tgg atg tca tgc gaa ggg gct Met Gly Leu Glu Thr Arg Ala Glu Thr Trp Met Ser Ser Glu Gly Ala	788
215 220 225	

294

tgg aag cat gct cag aga gta gag agc tgg ata ctc aga aac cca gga Trp Lys His Ala Gln Arg Val Glu Ser Trp Ile Leu Arg Asn Pro Gly 230 235 240 245	836
ttc gcg ctc ttg gca gga ttt atg gct tat atg att ggg caa aca gga Phe Ala Leu Leu Ala Gly Phe Met Ala Tyr Met Ile Gly Gln Thr Gly 250 255 260	884
atc cag cga act gtc ttc ttt gtc cta atg atg ctg gtc gcc cca tcc Ile Gln Arg Thr Val Phe Phe Val Leu Met Met Leu Val Ala Pro Ser 265 270 275	932
tac gga atg cga tgc gta gga gta gga aac aga gac ttt gtg gaa gga Tyr Gly Met Arg Cys Val Gly Val Gly Asn Arg Asp Phe Val Glu Gly 280 285 290	980
gtc tca ggt gga gca tgg gtc gat ctg gtg cta gaa cat gga gga tgc Val Ser Gly Gly Ala Trp Val Asp Leu Val Leu Glu His Gly Gly Cys 295 300 305	1028
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ggc aat ttg gtc caa att gag aac ctt gaa tac aca gtg gtt gta aca Gly Asn Leu Val Gln Ile Glu Asn Leu Glu Tyr Thr Val Val Val Thr 410 415 420	1364
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295

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Gly Val Thr Ala Thr Ile Thr Pro Arg Ser Pro Ser Val Glu Val Lys	
440 445 450	
ttg ccg gac tat gga gaa cta aca ctc gat tgt gaa ccc agg tct gga	1508
Leu Pro Asp Tyr Gly Glu Leu Thr Leu Asp Cys Glu Pro Arg Ser Gly	
455 460 465	
att gac ttt aat gag atg att ctg atg aaa atg aaa aag aaa aca tgg	1556
Ile Asp Phe Asn Glu Met Ile Leu Met Lys Met Lys Lys Lys Thr Trp	
470 475 480 485	
ctt gtg cat aag caa tgg ttt ttg gat cta cct cta cca tgg aca gca	1604
Leu Val His Lys Gln Trp Phe Leu Asp Leu Pro Leu Pro Trp Thr Ala	
490 495 500	
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Gly Ala Asp Thr Ser Glu Val His Trp Asn Tyr Lys Glu Arg Met Val	
505 510 515	
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Thr Phe Lys Val Pro His Ala Lys Arg Gln Asp Val Thr Val Leu Gly	
520 525 530	
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Ser Gln Glu Gly Ala Met His Ser Ala Leu Ala Gly Ala Thr Glu Val	
535 540 545	
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Asp Ser Gly Asp Gly Asn His Met Phe Ala Gly His Leu Lys Cys Lys	
550 555 560 565	
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Val Arg Met Glu Lys Leu Arg Ile Lys Gly Met Ser Tyr Thr Met Cys	
570 575 580	
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Ser Gly Lys Phe Ser Ile Asp Lys Glu Met Ala Glu Thr Gln His Gly	
585 590 595	
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Thr Thr Val Val Lys Val Lys Tyr Glu Gly Ala Gly Ala Pro Cys Lys	
600 605 610	
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Val Pro Ile Glu Ile Arg Asp Val Asn Lys Lys Lys Val Val Gly Arg	
615 620 625	
atc atc tca tcc acc cct ttg gct gag aat acc aac agt gca acc aac	2036
Ile Ile Ser Ser Thr Pro Leu Ala Glu Asn Thr Asn Ser Ala Thr Asn	
630 635 640 645	
ata gag tta gaa ccc ccc ttt ggg gac agc tac ata gtg ata ggt gtt	2084
Ile Glu Leu Glu Pro Pro Phe Gly Asp Ser Tyr Ile Val Ile Gly Val	
650 655 660	

296

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tca ttg gga aag gct gtg cac cag gtt ttt gga agt gtg tat aca acc Ser Leu Gly Lys Ala Val His Gln Val Phe Gly Ser Val Tyr Thr Thr 710 715 720 725	2276
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tgc ata gct gtt gga gga atc act ctg ttt ctg ggc ttc aca gtt caa Cys Ile Ala Val Gly Gly Ile Thr Leu Phe Leu Gly Phe Thr Val Gln 760 765 770	2420
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tac aaa ttt caa ccg gag tcc cca gcg aga cta gcg tct gca ata ttg Tyr Lys Phe Gln Pro Glu Ser Pro Ala Arg Leu Ala Ser Ala Ile Leu 810 815 820	2564
aat gcc cac aaa gat ggg gtc tgt gga att aga tca acc acg agg ctg Asn Ala His Lys Asp Gly Val Cys Gly Ile Arg Ser Thr Thr Arg Leu 825 830 835	2612
gaa aat gtc atg tgg aag caa ata acc aac gag cta aat tat gtt ctc Glu Asn Val Met Trp Lys Gln Ile Thr Asn Glu Leu Asn Tyr Val Leu 840 845 850	2660
tgg gaa gga gga cat gac ctc act gta gtg gct ggg gat gtg aag ggg Trp Glu Gly Gly His Asp Leu Thr Val Val Ala Gly Asp Val Lys Gly 855 860 865	2708

297

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gca aga aat agc aca ttt tta ata gac gga cca gac acc tcc gaa tgc Ala Arg Asn Ser Thr Phe Leu Ile Asp Gly Pro Asp Thr Ser Glu Cys 905 910 915	2852
ccc aat gaa cga aga gca tgg aac ttt ctt gag gtg gaa gac tat gga Pro Asn Glu Arg Arg Ala Trp Asn Phe Leu Glu Val Glu Asp Tyr Gly 920 925 930	2900
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ctg tgg ccc aag acc cac aca ttg tgg agc aat gga gtg ctg gaa agc Leu Trp Pro Lys Thr His Thr Leu Trp Ser Asn Gly Val Leu Glu Ser 1000 1005 1010	3140
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tac cgc cag ggc tat gcc acg caa acc gtg gcc cca tgg cac tta ggc Tyr Arg Gln Gly Tyr Ala Thr Gln Thr Val Gly Pro Trp His Leu Gly 1030 1035 1040 1045	3236
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cag gag gat tgt gac cat aga ggc cca tct ttg agg acc acc act gca Gln Glu Asp Cys Asp His Arg Gly Pro Ser Leu Arg Thr Thr Thr Ala 1065 1070 1075	3332
tct gga aaa cta gtc acg caa tgg tgc tgc cgc tcc tgc acg atg cct Ser Gly Lys Leu Val Thr Gln Trp Cys Cys Arg Ser Cys Thr Met Pro 1080 1085 1090	3380

298

ccc tta agg ttc ttg gga gaa gat ggg tgc tgg tat ggg atg gag att Pro Leu Arg Phe Leu Gly Glu Asp Gly Cys Trp Tyr Gly Met Glu Ile 1095 1100 1105	3428
agg ccc ttg agt gaa aaa gaa gag aac atg gtc aaa tca cag gta acg Arg Pro Leu Ser Glu Lys Glu Glu Asn Met Val Lys Ser Gln Val Thr 1110 1115 1120 1125	3476
gcc gga cag ggc aca tca gaa act ttt tct atg ggt ctg ttg tgc ctg Ala Gly Gln Gly Thr Ser Glu Thr Phe Ser Met Gly Leu Leu Cys Leu 1130 1135 1140	3524
acc ttg ttt gtg gaa gaa tgc ttg agg aga aga gtc act agg aaa cac Thr Leu Phe Val Glu Glu Cys Leu Arg Arg Arg Val Thr Arg Lys His 1145 1150 1155	3572
atg ata ttg gtt gtg gtg atc act ctt tgt gcc atc atc cta gga ggc Met Ile Leu Val Val Val Ile Thr Leu Cys Ala Ile Ile Leu Gly Gly 1160 1165 1170	3620
ctc aca tgg atg gac tta cta cga gcc ctc atc atg ttg ggg gac act Leu Thr Trp Met Asp Leu Leu Arg Ala Leu Ile Met Leu Gly Asp Thr 1175 1180 1185	3668
atg tct ggt aga ata gga gga cag atc cac cta gcc atc atg gca gtg Met Ser Gly Arg Ile Gly Gly Gln Ile His Leu Ala Ile Met Ala Val 1190 1195 1200 1205	3716
ttc aag atg tca cca gga tac gtg ctg ggt gtg ttt tta agg aaa ctc Phe Lys Met Ser Pro Gly Tyr Val Leu Gly Val Phe Leu Arg Lys Leu 1210 1215 1220	3764
act tca aga gag aca gca cta atg gta ata gga atg gcc atg aca acg Thr Ser Arg Glu Thr Ala Leu Met Val Ile Gly Met Ala Met Thr Thr 1225 1230 1235	3812
gtg ctt tca att cca cat gac ctt atg gaa ctc att gat gga ata tca Val Leu Ser Ile Pro His Asp Leu Met Glu Leu Ile Asp Gly Ile Ser 1240 1245 1250	3860
ctg ggg cta att ttg cta aaa ata gtg aca cat ttt gac aac acc caa Leu Gly Leu Ile Leu Leu Lys Ile Val Thr His Phe Asp Asn Thr Gln 1255 1260 1265	3908
gtg gga acc tta gcc ctt tcc ttg acc ttc ata aga tca aca atg cca Val Gly Thr Leu Ala Leu Ser Leu Thr Phe Ile Arg Ser Thr Met Pro 1270 1275 1280 1285	3956
ttg gtc atg gct tgg agg acc att atg gct gtg ttg ttt gtg gtc aca Leu Val Met Ala Trp Arg Thr Ile Met Ala Val Leu Phe Val Val Thr 1290 1295 1300	4004

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ctc att cct ttg tgc agg aca agc tgt ctt caa aaa cag tct cat tgg Leu Ile Pro Leu Cys Arg Thr Ser Cys Leu Gln Lys Gln Ser His Trp 1305 1310 1315	4052
gta gaa ata aca gca ctc atc cta gga gcc caa gct ctg cca gtg tac Val Glu Ile Thr Ala Leu Ile Leu Gly Ala Gln Ala Leu Pro Val Tyr 1320 1325 1330	4100
cta atg act ctt atg aaa gga gcc tca aga aga tct tgg cct ctt aac Leu Met Thr Leu Met Lys Gly Ala Ser Arg Arg Ser Trp Pro Leu Asn 1335 1340 1345	4148
gag ggc ata atg gct gtg ggt ttg gtt agt ctc tta gga agc gct ctt Glu Gly Ile Met Ala Val Gly Leu Val Ser Leu Leu Gly Ser Ala Leu 1350 1355 1360 1365	4196
tta aag aat gat gtc cct tta gct ggc cca atg gtg gca gga ggc tta Leu Lys Asn Asp Val Pro Leu Ala Gly Pro Met Val Ala Gly Gly Leu 1370 1375 1380	4244
ctt ctg gcg gct tac gtg atg agt ggt agc tca gca gat ctg tca cta Leu Leu Ala Ala Tyr Val Met Ser Gly Ser Ser Ala Asp Leu Ser Leu 1385 1390 1395	4292
gag aag gcc gcc aat gtg cag tgg gat gaa atg gca gac ata aca ggc Glu Lys Ala Ala Asn Val Gln Trp Asp Glu Met Ala Asp Ile Thr Gly 1400 1405 1410	4340
tca agc cca atc ata gaa gtg aag cag gat gaa gat ggc tct ttc tcc Ser Ser Pro Ile Ile Glu Val Lys Gln Asp Glu Asp Gly Ser Phe Ser 1415 1420 1425	4388
ata cgg gac gtc gag gaa acc aat atg ata acc ctt ttg gtg aaa ctg Ile Arg Asp Val Glu Glu Thr Asn Met Ile Thr Leu Leu Val Lys Leu 1430 1435 1440 1445	4436
gca ctg ata aca gtg tca ggt ctc tac ccc ttg gca att cca gtc aca Ala Leu Ile Thr Val Ser Gly Leu Tyr Pro Leu Ala Ile Pro Val Thr 1450 1455 1460	4484
atg acc tta tgg tac atg tgg caa gtg aaa aca caa aga tca gga gcc Met Thr Leu Trp Tyr Met Trp Gln Val Lys Thr Gln Arg Ser Gly Ala 1465 1470 1475	4532
ctg tgg gac gtc ccc tca ccc gct gcc act caa aaa gcc gca ctg tct Leu Trp Asp Val Pro Ser Pro Ala Ala Thr Gln Lys Ala Ala Leu Ser 1480 1485 1490	4580
gaa gga gtg tac agg atc atg caa aga ggg tta ttt ggg aaa act cag Glu Gly Val Tyr Arg Ile Met Gln Arg Gly Leu Phe Gly Lys Thr Gln 1495 1500 1505	4628
gtt gga gta ggg ata cac atg gaa ggt gta ttt cac aca atg tgg cat Val Gly Val Gly Ile His Met Glu Gly Val Phe His Thr Met Trp His 1510 1515 1520 1525	4676

300

gta aca aga gga tca gtg atc tgc cat gag act ggg aga ttg gag cca Val Thr Arg Gly Ser Val Ile Cys His Glu Thr Gly Arg Leu Glu Pro 1530 1535 1540	4724
tct tgg gct gac gtc agg aat gac atg ata tca tac ggt ggg gga tgg Ser Trp Ala Asp Val Arg Asn Asp Met Ile Ser Tyr Gly Gly Gly Trp 1545 1550 1555	4772
aga ctt gga gac aaa tgg gac aaa gaa gaa gat gtt cag gtc ctc gcc Arg Leu Gly Asp Lys Trp Asp Lys Glu Glu Asp Val Gln Val Leu Ala 1560 1565 1570	4820
ata gaa cca gga aaa aat cct aaa cat gtc caa acg aaa ccc ggc ctt Ile Glu Pro Gly Lys Asn Pro Lys His Val Gln Thr Lys Pro Gly Leu 1575 1580 1585	4868
ttc aag acc cta act gga gaa att gga gca gta aca tta gat ttc aaa Phe Lys Thr Leu Thr Gly Glu Ile Gly Ala Val Thr Leu Asp Phe Lys 1590 1595 1600 1605	4916
ccc gga acg tct ggt tct ccc atc atc aac agg aaa gga aaa gtc atc Pro Gly Thr Ser Gly Ser Pro Ile Ile Asn Arg Lys Gly Lys Val Ile 1610 1615 1620	4964
gga ctc tat gga aat gga gta gtt acc aaa tca ggt gat tac gtc agt Gly Leu Tyr Gly Asn Gly Val Val Thr Lys Ser Gly Asp Tyr Val Ser 1625 1630 1635	5012
gcc ata acg caa gcc gaa aga att gga gag cca gat tat gaa gtg gat Ala Ile Thr Gln Ala Glu Arg Ile Gly Glu Pro Asp Tyr Glu Val Asp 1640 1645 1650	5060
gag gac att ttt cga aag aaa aga tta act ata atg gac tta cac ccc Glu Asp Ile Phe Arg Lys Lys Arg Leu Thr Ile Met Asp Leu His Pro 1655 1660 1665	5108
gga gct gga aag aca aaa aga att ctt cca tca ata gtg aga gaa gcc Gly Ala Gly Lys Thr Lys Arg Ile Leu Pro Ser Ile Val Arg Glu Ala 1670 1675 1680 1685	5156
tta aaa agg agg ctg cga acc ttg att ttg gct ccc acg aga gtg gtg Leu Lys Arg Arg Leu Arg Thr Leu Ile Leu Ala Pro Thr Arg Val Val 1690 1695 1700	5204
gcg gcc gag atg gaa gag gcc cta cgt gga ctg cca atc cgt tat cag Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu Pro Ile Arg Tyr Gln 1705 1710 1715	5252
acc cca gct gtg aaa tca gaa cac aca gga aga gag att gta gac ctc Thr Pro Ala Val Lys Ser Glu His Thr Gly Arg Glu Ile Val Asp Leu 1720 1725 1730	5300

301

atg tgt cat gca acc ttc aca aca aga ctt ttg tca tca acc aga gtt Met Cys His Ala Thr Phe Thr Thr Arg Leu Leu Ser Ser Thr Arg Val 1735 1740 1745	5348
cca aat tac aac ctc ata gtg atg gat gaa gca cat ttc acc gat cct Pro Asn Tyr Asn Leu Ile Val Met Asp Glu Ala His Phe Thr Asp Pro 1750 1755 1760 1765	5396
tct agt gtc gcg gct aga gga tac atc tcg acc agg gtg gaa atg gga Ser Ser Val Ala Ala Arg Gly Tyr Ile Ser Thr Arg Val Glu Met Gly 1770 1775 1780	5444
gag gca gca gcc atc ttc atg acc gca acc cct ccc gga gcg aca gat Glu Ala Ala Ala Ile Phe Met Thr Ala Thr Pro Pro Gly Ala Thr Asp 1785 1790 1795	5492
ccc ttt ccc cag agc aac agc cca ata gaa gac atc gag agg gaa att Pro Phe Pro Gln Ser Asn Ser Pro Ile Glu Asp Ile Glu Arg Glu Ile 1800 1805 1810	5540
ccg gaa agg tca tgg aac aca ggg ttc gac tgg ata aca gac tac caa Pro Glu Arg Ser Trp Asn Thr Gly Phe Asp Trp Ile Thr Asp Tyr Gln 1815 1820 1825	5588
ggg aaa act gtg tgg ttt gtt ccc agc ata aaa gct gga aat gac att Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile 1830 1835 1840 1845	5636
gca aat tgt ttg aga aag tcg gga aag aaa gtt atc cag ttg agt agg Ala Asn Cys Leu Arg Lys Ser Gly Lys Val Ile Gln Leu Ser Arg 1850 1855 1860	5684
aaa acc ttt gat aca gag tat cca aaa acg aaa ctc acg gac tgg gat Lys Thr Phe Asp Thr Glu Tyr Pro Lys Thr Lys Leu Thr Asp Trp Asp 1865 1870 1875	5732
ttt gtg gtc act aca gac ata tct gaa atg ggg gcc aat ttt aga gct Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Arg Ala 1880 1885 1890	5780
ggg aga gtg ata gac cct agg aga tgc ctc aag cca gtt atc cta aca Gly Arg Val Ile Asp Pro Arg Arg Cys Leu Lys Pro Val Ile Leu Thr 1895 1900 1905	5828
gat ggg cca gag aga gtc att tta gca ggt cct att cca gtg act cca Asp Gly Pro Glu Arg Val Ile Leu Ala Gly Pro Ile Pro Val Thr Pro 1910 1915 1920 1925	5876
gca agc gct gct cag aga aga ggg cga ata gga agg aac cca gca caa Ala Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro Ala Gln 1930 1935 1940	5924
gaa gac gac caa tac gtt ttc tcc gga gac cca cta aaa aat gat gaa Glu Asp Asp Gln Tyr Val Phe Ser Gly Asp Pro Leu Lys Asn Asp Glu 1945 1950 1955	5972

302

gat cat gcc cac tgg aca gaa gca aag atg ctg ctt gac aat atc tac Asp His Ala His Trp Thr Glu Ala Lys Met Leu Leu Asp Asn Ile Tyr 1960 1965 1970	6020
acc cca gaa ggg atc att cca aca ttg ttt ggt ccg gaa agg gaa aaa Thr Pro Glu Gly Ile Ile Pro Thr Leu Phe Gly Pro Glu Arg Glu Lys 1975 1980 1985	6068
acc caa gcc att gat gga gag ttt cgc ctc aga ggg gaa caa agg aag Thr Gln Ala Ile Asp Glu Phe Arg Leu Arg Gly Glu Gln Arg Lys 1990 1995 2000 2005	6116
act ttt gtg gaa tta atg agg aga gga gac ctt ccg gtg tgg ctg agc Thr Phe Val Glu Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ser 2010 2015 2020	6164
tat aag gta gct tct gct ggc att tct tac aaa gat ccg gaa tgg tgc Tyr Lys Val Ala Ser Ala Gly Ile Ser Tyr Lys Asp Arg Glu Trp Cys 2025 2030 2035	6212
ttc aca ggg gaa agg aat aac caa att tta gaa gaa aac atg gag gtt Phe Thr Gly Glu Arg Asn Asn Gln Ile Leu Glu Glu Asn Met Glu Val 2040 2045 2050	6260
gaa att tgg act aga gag gga gaa aag aaa aag cta agg cca aga tgg Glu Ile Trp Thr Arg Glu Gly Glu Lys Lys Lys Leu Arg Pro Arg Trp 2055 2060 2065	6308
tta gat gca cgt gta tac gct gac ccc atg gct ttg aag gat ttt aag Leu Asp Ala Arg Val Tyr Ala Asp Pro Met Ala Leu Lys Asp Phe Lys 2070 2075 2080 2085	6356
gag ttt gct agt gga agg aag agc ata act ctc gac atc cta aca gag Glu Phe Ala Ser Gly Arg Lys Ser Ile Thr Leu Asp Ile Leu Thr Glu 2090 2095 2100	6404
att gcc agt ttg cca act tac ctt tcc tct agg gcc aag ctc gcc ctt Ile Ala Ser Leu Pro Thr Tyr Leu Ser Ser Arg Ala Lys Leu Ala Leu 2105 2110 2115	6452
gat aac ata gtc atg ctc cac aca aca gaa aga gga ggg agg gcc tac Asp Asn Ile Val Met Leu His Thr Thr Glu Arg Gly Gly Arg Ala Tyr 2120 2125 2130	6500
caa cac gcc ctg aac gaa ctc ccg gag tca ctg gaa aca ctt atg ctt Gln His Ala Leu Asn Glu Leu Pro Glu Ser Leu Glu Thr Leu Met Leu 2135 2140 2145	6548
gta gct tta cta ggt gct atg aca gca ggt atc ttc ctg ttt ttc atg Val Ala Leu Leu Gly Ala Met Thr Ala Gly Ile Phe Leu Phe Phe Met 2150 2155 2160 2165	6596

303

caa ggg aaa gga ata ggg aaa ttg tca atg ggt ttg ata acc att gcg Gln Gly Lys Gly Ile Gly Lys Leu Ser Met Gly Leu Ile Thr Ile Ala 2170 2175 2180	6644
gtg gct agt ggc ttg ttc tgg gta gca gaa att caa ccc cag tgg ata Val Ala Ser Gly Leu Phe Trp Val Ala Glu Ile Gln Pro Gln Trp Ile 2185 2190 2195	6692
gcg gcc tca atc ata cta gag ttt ttt ctc atg gta ctg ttg ata ccg Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Met Val Leu Leu Ile Pro 2200 2205 2210	6740
gaa cca gaa aaa caa agg acc cca caa gac aat caa ttg atc tac gtc Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn Gln Leu Ile Tyr Val 2215 2220 2225	6788
ata ttg acc att ctc acc att att ggt ctc ata gca gcc aac gag atg Ile Leu Thr Ile Leu Thr Ile Ile Gly Leu Ile Ala Ala Asn Glu Met 2230 2235 2240 2245	6836
ggg ctg att gaa aaa aca aaa acg gat ttt ggg ttt tac cag gta aaa Gly Leu Ile Glu Lys Thr Lys Thr Asp Phe Gly Phe Tyr Gln Val Lys 2250 2255 2260	6884
aca gaa acc acc atc ctc gat gtg gac ttg aga cca gct tca gca tgg Thr Glu Thr Thr Ile Leu Asp Val Asp Leu Arg Pro Ala Ser Ala Trp 2265 2270 2275	6932
acg ctc tat gca gta gcc acc aca ttt ctg act ccc atg ctg aga cac Thr Leu Tyr Ala Val Ala Thr Thr Phe Leu Thr Pro Met Leu Arg His 2280 2285 2290	6980
acc ata gaa aac acg tcg gcc aac cta tct cta gca gcc att gcc aac Thr Ile Glu Asn Thr Ser Ala Asn Leu Ser Leu Ala Ala Ile Ala Asn 2295 2300 2305	7028
cag gcg gcc gtc cta atg ggg ctt gga aaa gga tgg ccg ctc cac aga Gln Ala Ala Val Leu Met Gly Leu Gly Lys Trp Pro Leu His Arg 2310 2315 2320 2325	7076
atg gac ctc ggt gtg ccg ctg tta gca atg gga tgc tat tct caa gtg Met Asp Leu Gly Val Pro Leu Leu Ala Met Gly Cys Tyr Ser Gln Val 2330 2335 2340	7124
aac cca aca act ttg aca gca tcc tta gtc atg ctt tca gtc cat tat Asn Pro Thr Thr Leu Thr Ala Ser Leu Val Met Leu Ser Val His Tyr 2345 2350 2355	7172
gca ata ata ggt cca gga ttg cag gca aaa gcc aca aga gag gcc cag Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg Glu Ala Gln 2360 2365 2370	7220
aaa agg aca gct gct ggg atc atg aaa aac ccc acg gtg gac ggg ata Lys Arg Thr Ala Ala Gly Ile Met Lys Asn Pro Thr Val Asp Gly Ile 2375 2380 2385	7268

304

aca gta ata gat cta gaa cca ata tcc tat gac cca aaa ttt gaa aag Thr Val Ile Asp Leu Glu Pro Ile Ser Tyr Asp Pro Lys Phe Glu Lys 2390 2395 2400 2405	7316
caa tta ggg cag gtc atg cta ctc gtc ttg tgt gct gga caa cta ctc Gln Leu Gly Gln Val Met Leu Leu Val Leu Cys Ala Gly Gln Leu Leu 2410 2415 2420	7364
ttg atg aga aca aca tgg gct ttc tgt gaa gtc ttg act ttg gcc aca Leu Met Arg Thr Thr Trp Ala Phe Cys Glu Val Leu Thr Leu Ala Thr 2425 2430 2435	7412
gga cca atc ttg acc ttg tgg gag ggc aac ccg gga agg ttt tgg aac Gly Pro Ile Leu Thr Leu Trp Glu Gly Asn Pro Gly Arg Phe Trp Asn 2440 2445 2450	7460
acg acc ata gcc gta tcc acc gcc aac att ttc agg gga agt tac ctg Thr Thr Ile Ala Val Ser Thr Ala Asn Ile Phe Arg Gly Ser Tyr Leu 2455 2460 2465	7508
gcg gga gct gga ctg gct ttt tca ctc ata aag aat gta caa acc cct Ala Gly Ala Gly Leu Ala Phe Ser Leu Ile Lys Asn Val Gln Thr Pro 2470 2475 2480 2485	7556
agg agg gga act ggg acc aca gga gag aca ctg gga gag aag tgg aag Arg Arg Gly Thr Gly Thr Thr Gly Glu Thr Leu Gly Glu Lys Trp Lys 2490 2495 2500	7604
aga cag cta aac tca tta tac aga aaa gag ttt gaa gag tat aaa aga Arg Gln Leu Asn Ser Leu Tyr Arg Lys Glu Phe Glu Glu Tyr Lys Arg 2505 2510 2515	7652
agt gga ata cta gaa gtg gac agg act gaa gcc aag tct gcc ctg aaa Ser Gly Ile Leu Glu Val Asp Arg Thr Glu Ala Lys Ser Ala Leu Lys 2520 2525 2530	7700
gat ggg tct aaa atc aag cat gca gta tct aga ggg tcc agt aag att Asp Gly Ser Lys Ile Lys His Ala Val Ser Arg Gly Ser Ser Lys Ile 2535 2540 2545	7748
aga tgg att gtt gag aga ggg atg gta aag cca aaa ggg aaa gtt gta Arg Trp Ile Val Glu Arg Gly Met Val Lys Pro Lys Gly Lys Val Val 2550 2555 2560 2565	7796
gat ctt ggc tgt ggg aga gga gga tgg tct tat tac atg gcg acg ctc Asp Leu Gly Cys Gly Arg Gly Gly Trp Ser Tyr Tyr Met Ala Thr Leu 2570 2575 2580	7844
aag aac gtg act gaa gtg aaa ggg tat aca aaa gga ggt cca gga cat Lys Asn Val Thr Glu Val Lys Gly Tyr Thr Lys Gly Gly Pro Gly His 2585 2590 2595	7892

305

gaa gaa ccg att ccc atg gct act tat ggc tgg aat ttg gtc aaa ctc Glu Glu Pro Ile Pro Met Ala Thr Tyr Gly Trp Asn Leu Val Lys Leu 2600 2605 2610	7940
cat tca ggg gtt gac gtg ttc tac aaa ccc aca gag caa gtg gac acc His Ser Gly Val Asp Val Phe Tyr Lys Pro Thr Glu Gln Val Asp Thr 2615 2620 2625	7988
ctg ctc tgt gat att ggg gag tca tct tct aat cca aca ata gag gaa Leu Leu Cys Asp Ile Gly Glu Ser Ser Ser Asn Pro Thr Ile Glu Glu 2630 2635 2640 2645	8036
gga aga aca tta aga gtt ttg aag atg gtg gag cca tgg ctc tct tca Gly Arg Thr Leu Arg Val Leu Lys Met Val Glu Pro Trp Leu Ser Ser 2650 2655 2660	8084
aaa cct gaa ttc tgc atc aaa gtc ett aac ccc tac atg cca aca gtc Lys Pro Glu Phe Cys Ile Lys Val Leu Asn Pro Tyr Met Pro Thr Val 2665 2670 2675	8132
ata gaa gag ctg gag aaa ctg cag aga aaa cat ggt ggg aac ctt gtc Ile Glu Glu Leu Glu Lys Leu Gln Arg Lys His Gly Gly Asn Leu Val 2680 2685 2690	8180
aga tgc ccg ctg tcc agg aac tcc acc cat gag atg tat tgg gtg tca Arg Cys Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr Trp Val Ser 2695 2700 2705	8228
gga gcg tcg gga aac att gtg agc tct gtg aac aca aca tca aag atg Gly Ala Ser Gly Asn Ile Val Ser Ser Val Asn Thr Thr Ser Lys Met 2710 2715 2720 2725	8276
ttg ttg aac agg ttc aca aca agg cat agg aaa ccc act tat gag aag Leu Leu Asn Arg Phe Thr Thr Arg His Arg Lys Pro Thr Tyr Glu Lys 2730 2735 2740	8324
gac gta gat ctt ggg gca gga acg aga agt gtc tcc act gaa aca gaa Asp Val Asp Leu Gly Ala Gly Thr Arg Ser Val Ser Thr Glu Thr Glu 2745 2750 2755	8372
aaa cca gac atg aca att att ggg aga agg ctt cag cga ttg caa gag Lys Pro Asp Met Thr Ile Ile Gly Arg Arg Leu Gln Arg Leu Gln Glu 2760 2765 2770	8420
gag cac aaa gaa acc tgg cat tat gat cag gaa aac cca tac aga acc Glu His Lys Glu Thr Trp His Tyr Asp Gln Glu Asn Pro Tyr Arg Thr 2775 2780 2785	8468
tgg gcg tat cat gga agc tat gaa gct cct tcg aca ggc tct gca tcc Trp Ala Tyr His Gly Ser Tyr Glu Ala Pro Ser Thr Gly Ser Ala Ser 2790 2795 2800 2805	8516
tcc atg gtg aac ggg gta gta aaa ctg cta aca aaa cct tgg gat gtg Ser Met Val Asn Gly Val Val Lys Leu Leu Thr Lys Pro Trp Asp Val 2810 2815 2820	8564

306

gtt cca atg gtg acc cag tta gcc atg aca gac aca acc cct ttt ggg Val Pro Met Val Thr Gln Leu Ala Met Thr Asp Thr Thr Pro Phe Gly 2825 2830 2835	8612
caa caa aga gtg ttc aaa gag aag gtg gat acc aga aca cca caa cca Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr Arg Thr Pro Gln Pro 2840 2845 2850	8660
aaa ccc ggt aca cga atg gtt atg acc acg aca gcc aat tgg ctg tgg Lys Pro Gly Thr Arg Met Val Met Thr Thr Thr Ala Asn Trp Leu Trp 2855 2860 2865	8708
gcc ctg ctt ggg aag aag aaa aat ccc aga ctg tgc aca agg gaa gag Ala Leu Leu Gly Lys Lys Lys Asn Pro Arg Leu Cys Thr Arg Glu Glu 2870 2875 2880 2885	8756
ttc atc tca aaa gtt aga tca aac gca gcc ata ggc gca gtc ttt cag Phe Ile Ser Lys Val Arg Ser Asn Ala Ala Ile Gly Ala Val Phe Gln 2890 2895 2900	8804
gaa gaa cag gga tgg aca tca gcc agt gaa gct gtg aat gac agc cgg Glu Glu Gln Gly Trp Thr Ser Ala Ser Glu Ala Val Asn Asp Ser Arg 2905 2910 2915	8852
ttt tgg gaa ctg gtt gac aaa gaa agg gcc cta cac cag gaa ggg aaa Phe Trp Glu Leu Val Asp Lys Glu Arg Ala Leu His Gln Glu Gly Lys 2920 2925 2930	8900
tgt gaa tgg tgt gtc tac aac atg atg gga aaa cgt gag aaa aag tta Cys Glu Ser Cys Val Tyr Asn Met Met Gly Lys Arg Glu Lys Lys Leu 2935 2940 2945	8948
gga gag ttt ggc aga gcc aag gga agc cga gca atc tgg tac atg tgg Gly Glu Phe Gly Arg Ala Lys Gly Ser Arg Ala Ile Trp Tyr Met Trp 2950 2955 2960 2965	8996
ctg gga gcg cgg ttt ctg gaa ttt gaa gcc ctg ggt ttt ttg aat gaa Leu Gly Ala Arg Phe Leu Glu Phe Glu Ala Leu Gly Phe Leu Asn Glu 2970 2975 2980	9044
gat cac tgg ttt ggc aga gaa aat tca tgg agt gga gtg gaa ggg gaa Asp His Trp Phe Gly Arg Glu Asn Ser Trp Ser Gly Val Glu Gly Glu 2985 2990 2995	9092
ggt ctg cac aga ttg gga tat atc ctg gag gag ata gac aag aag gat Gly Leu His Arg Leu Gly Tyr Ile Leu Glu Glu Ile Asp Lys Lys Asp 3000 3005 3010	9140
gga gac cta atg tat gct gat gac aca gca gcc tgg gac aca aga atc Gly Asp Leu Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp Thr Arg Ile 3015 3020 3025	9188

307

act gag gat gac ctt caa aat gaa gaa ctg atc acg gaa cag atg gcc Thr Glu Asp Asp Leu Gln Asn Glu Glu Leu Ile Thr Glu Gln Met Ala 3030 3035 3040 3045	9236
ccc cac cac aag atc cta gcc aaa gcc att ttc aaa cta acc tat caa Pro His His Lys Ile Leu Ala Lys Ala Ile Phe Lys Leu Thr Tyr Gln 3050 3055 3060	9284
aac aaa gtg gtg aaa gtc ctc aga ccc aca ccg aga gga gcg gtg atg Asn Lys Val Val Lys Val Leu Arg Pro Thr Pro Arg Gly Ala Val Met 3065 3070 3075	9332
gat atc ata tcc agg aaa gac caa aga ggt agt gga caa gtt gga aca Asp Ile Ile Ser Arg Lys Asp Gln Arg Gly Ser Gly Gln Val Gly Thr 3080 3085 3090	9380
tat ggt ttg aac aca ttc acc aac atg gaa gtt caa ctc atc cgc caa Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Val Gln Leu Ile Arg Gln 3095 3100 3105	9428
atg gaa gct gaa gga gtc atc aca caa gat gac atg cag aac cca aaa Met Glu Ala Glu Gly Val Ile Thr Gln Asp Asp Met Gln Asn Pro Lys 3110 3115 3120 3125	9476
ggg ttg aaa gaa aga gtt gag aaa tgg ctg aaa gag tgt ggt gtc gac Gly Leu Lys Glu Arg Val Glu Lys Trp Leu Lys Glu Cys Gly Val Asp 3130 3135 3140	9524
agg tta aag agg atg gca atc agt gga gac gat tgc gtg gtg aag ccc Arg Leu Lys Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val Lys Pro 3145 3150 3155	9572
ctg gat gag agg ttt ggc act tcc ctc ctc ttc ttg aac gac atg gga Leu Asp Glu Arg Phe Gly Thr Ser Leu Leu Phe Leu Asn Asp Met Gly 3160 3165 3170	9620
aag gtg agg aaa gac att ccg cag tgg gaa cca tct aag gga tgg aaa Lys Val Arg Lys Asp Ile Pro Gln Trp Glu Pro Ser Lys Gly Trp Lys 3175 3180 3185	9668
aac tgg caa gag gtt cct ttt tgc tcc cac cac ttt cac aag atc ttc Asn Trp Gln Glu Val Pro Phe Cys Ser His His Phe His Lys Ile Phe 3190 3195 3200 3205	9716
atg aag gat ggc cgc tca cta gtt gtt cca tgt aga aac cag gat gaa Met Lys Asp Gly Arg Ser Leu Val Val Pro Cys Arg Asn Gln Asp Glu 3210 3215 3220	9764
ctg ata ggg aga gcc aga atc tgc cag ggg gct gga tgg agc tta aga Leu Ile Gly Arg Ala Arg Ile Ser Gln Gly Ala Gly Trp Ser Leu Arg 3225 3230 3235	9812
gaa aca gcc tgc ctg ggc aaa gct tac gcc cag atg tgg tgc ctc atg Glu Thr Ala Cys Leu Gly Lys Ala Tyr Ala Gln Met Trp Ser Leu Met 3240 3245 3250	9860

308

tac ttc cac aga agg gat ctg cgt tta gcc tcc atg gcc ata tgc tca	9908
Tyr Phe His Arg Arg Asp Leu Arg Leu Ala Ser Met Ala Ile Cys Ser	
3255 3260 3265	
gca gtt cca acg gaa tgg ttt cca aca agc aga aca aca tgg tca atc	9956
Ala Val Pro Thr Glu Trp Phe Pro Thr Ser Arg Thr Thr Trp Ser Ile	
3270 3275 3280 3285	
cac gct cat cat cag tgg atg acc act gaa gat atg ctc aaa gtg tgg	10004
His Ala His His Gln Trp Met Thr Thr Glu Asp Met Leu Lys Val Trp	
3290 3295 3300	
aac aga gtg tgg ata gaa gac aac cct aat atg act gac aag act cca	10052
Asn Arg Val Trp Ile Glu Asp Asn Pro Asn Met Thr Asp Lys Thr Pro	
3305 3310 3315	
gtc cat tog tgg gaa gat ata cct tac cta ggg aaa aga gag gat ttg	10100
Val His Ser Trp Glu Asp Ile Pro Tyr Leu Gly Lys Arg Glu Asp Leu	
3320 3325 3330	
tgg tgt gga tcc ctg att gga ctt tct tcc aga gcc acc tgg gcg aag	10148
Trp Cys Gly Ser Leu Ile Gly Leu Ser Ser Arg Ala Thr Trp Ala Lys	
3335 3340 3345	
aac att cac acg gcc ata acc cag gtc aga aac ctg atc gga aaa gag	10196
Asn Ile His Thr Ala Ile Thr Gln Val Arg Asn Leu Ile Gly Lys Glu	
3350 3355 3360 3365	
gaa tac gtg gat tac atg cca gta atg aaa aga tac agc gct cct tca	10244
Glu Tyr Val Asp Tyr Met Pro Val Met Lys Arg Tyr Ser Ala Pro Ser	
3370 3375 3380	
gag agt gaa gga gtt ctg taa ttaccaacaa caaacaccaa aggctattga	10295
Glu Ser Glu Gly Val Leu *	
3385	
agtccaggcca cttgtgccac ggcttgagca aaccgtgctg cctgtagctc cgccaataat	10355
gggaggcgtg aaatccctag ggaggccatg cgccacggaa gctgtacgcg tggcatattg	10415
gactagcggg tagaggagac ccctcccatc actgacaaaa cgcagcaaaa gggggcccga	10475
agccaggagg aagctgtact cctggtggaa ggactagagg ttagaggaga ccccccaac	10535
acaaaaacag catattgacg ctgggaaaga ccagagatcc tgctgtctct gcaacatcaa	10595
tccaggcaca gacgaagca agatggattg gtgttggtga tccaacaggg tct	10648
<210> 26	
<211> 3387	
<212> PRT	
<213> Artificial Sequence	
<220>	
<223> Description of Artificial Sequence:/Note =	
synthetic construct	

<400> 26

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Met	Asn	Gln	Arg	Lys	Lys	Val	Val	Arg	Pro	Pro	Phe	Asn	Met	Leu	Lys	
1				5					10					15		
Arg	Glu	Arg	Asn	Arg	Val	Ser	Thr	Pro	Gln	Gly	Leu	Val	Lys	Arg	Phe	
			20					25					30			
Ser	Thr	Gly	Leu	Phe	Ser	Gly	Lys	Gly	Pro	Leu	Arg	Met	Val	Leu	Ala	
		35				40						45				
Phe	Ile	Thr	Phe	Leu	Arg	Val	Leu	Ser	Ile	Pro	Pro	Thr	Ala	Gly	Ile	
	50				55					60						
Leu	Lys	Arg	Trp	Gly	Gln	Leu	Lys	Lys	Asn	Lys	Ala	Ile	Arg	Ile	Leu	
65				70					75					80		
Ile	Gly	Phe	Arg	Lys	Glu	Ile	Gly	Arg	Met	Leu	Asn	Ile	Leu	Asn	Gly	
			85					90					95			
Arg	Lys	Arg	Ser	Thr	Ile	Thr	Leu	Leu	Cys	Leu	Ile	Pro	Thr	Val	Met	
		100					105						110			
Ala	Phe	His	Leu	Ser	Thr	Arg	Asp	Gly	Glu	Pro	Leu	Met	Ile	Val	Ala	
	115					120						125				
Lys	His	Glu	Arg	Gly	Arg	Pro	Leu	Leu	Phe	Lys	Thr	Thr	Glu	Gly	Ile	
	130				135						140					
Asn	Lys	Cys	Thr	Leu	Ile	Ala	Met	Asp	Leu	Gly	Glu	Met	Cys	Glu	Asp	
145				150					155					160		
Thr	Val	Thr	Tyr	Lys	Cys	Pro	Leu	Leu	Val	Asn	Thr	Glu	Pro	Glu	Asp	
			165					170						175		
Ile	Asp	Cys	Trp	Cys	Asn	Leu	Thr	Ser	Thr	Trp	Val	Met	Tyr	Gly	Thr	
	180							185					190			
Cys	Thr	Gln	Ser	Gly	Glu	Arg	Arg	Arg	Glu	Lys	Arg	Ser	Val	Ala	Leu	
	195					200						205				
Thr	Pro	His	Ser	Gly	Met	Gly	Leu	Glu	Thr	Arg	Ala	Glu	Thr	Trp	Met	
	210				215						220					
Ser	Ser	Glu	Gly	Ala	Trp	Lys	His	Ala	Gln	Arg	Val	Glu	Ser	Trp	Ile	
225				230						235				240		
Leu	Arg	Asn	Pro	Gly	Phe	Ala	Leu	Leu	Ala	Gly	Phe	Met	Ala	Tyr	Met	
			245					250					255			
Ile	Gly	Gln	Thr	Gly	Ile	Gln	Arg	Thr	Val	Phe	Phe	Val	Leu	Met	Met	
	260							265				270				
Leu	Val	Ala	Pro	Ser	Tyr	Gly	Met	Arg	Cys	Val	Gly	Val	Gly	Asn	Arg	
	275					280						285				
Asp	Phe	Val	Glu	Gly	Val	Ser	Gly	Gly	Ala	Trp	Val	Asp	Leu	Val	Leu	
	290				295						300					
Glu	His	Gly	Gly	Cys	Val	Thr	Thr	Met	Ala	Gln	Gly	Lys	Pro	Thr	Leu	
305				310					315					320		
Asp	Phe	Glu	Leu	Thr	Lys	Thr	Thr	Ala	Lys	Glu	Val	Ala	Leu	Leu	Arg	
			325					330					335			
Thr	Tyr	Cys	Ile	Glu	Ala	Ser	Ile	Ser	Asn	Ile	Thr	Thr	Ala	Thr	Arg	
	340						345						350			
Cys	Pro	Thr	Gln	Gly	Glu	Pro	Tyr	Leu	Lys	Glu	Glu	Gln	Asp	Gln	Gln	
	355					360						365				
Tyr	Ile	Cys	Arg	Arg	Asp	Val	Val	Asp	Arg	Gly	Trp	Gly	Asn	Gly	Cys	
	370				375						380					
Gly	Leu	Phe	Gly	Lys	Gly	Gly	Val	Val	Thr	Cys	Ala	Lys	Phe	Ser	Cys	
385				390					395					400		
Ser	Gly	Lys	Ile	Thr	Gly	Asn	Leu	Val	Gln	Ile	Glu	Asn	Leu	Glu	Tyr	
			405						410					415		
Thr	Val	Val	Val	Thr	Val	His	Asn	Gly	Asp	Thr	His	Ala	Val	Gly	Asn	
	420							425					430			

310

Asp Thr Ser Asn His Gly Val Thr Ala Thr Ile Thr Pro Arg Ser Pro
 435 440 445
 Ser Val Glu Val Lys Leu Pro Asp Tyr Gly Glu Leu Thr Leu Asp Cys
 450 455 460
 Glu Pro Arg Ser Gly Ile Asp Phe Asn Glu Met Ile Leu Met Lys Met
 465 470 475 480
 Lys Lys Lys Thr Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu Pro
 485 490 495
 Leu Pro Trp Thr Ala Gly Ala Asp Thr Ser Glu Val His Trp Asn Tyr
 500 505 510
 Lys Glu Arg Met Val Thr Phe Lys Val Pro His Ala Lys Arg Gln Asp
 515 520 525
 Val Thr Val Leu Gly Ser Gln Glu Gly Ala Met His Ser Ala Leu Ala
 530 535 540
 Gly Ala Thr Glu Val Asp Ser Gly Asp Gly Asn His Met Phe Ala Gly
 545 550 555 560
 His Leu Lys Cys Lys Val Arg Met Glu Lys Leu Arg Ile Lys Gly Met
 565 570 575
 Ser Tyr Thr Met Cys Ser Gly Lys Phe Ser Ile Asp Lys Glu Met Ala
 580 585 590
 Glu Thr Gln His Gly Thr Thr Val Val Lys Val Lys Tyr Glu Gly Ala
 595 600 605
 Gly Ala Pro Cys Lys Val Pro Ile Glu Ile Arg Asp Val Asn Lys Lys
 610 615 620
 Lys Val Val Gly Arg Ile Ile Ser Ser Thr Pro Leu Ala Glu Asn Thr
 625 630 635 640
 Asn Ser Ala Thr Asn Ile Glu Leu Glu Pro Pro Phe Gly Asp Ser Tyr
 645 650 655
 Ile Val Ile Gly Val Gly Asn Ser Ala Leu Thr Leu His Trp Phe Arg
 660 665 670
 Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ser Thr Tyr Arg Gly Ala
 675 680 685
 Lys Arg Met Ala Ile Leu Gly Glu Thr Ala Trp Asp Phe Gly Ser Val
 690 695 700
 Gly Gly Leu Phe Thr Ser Leu Gly Lys Ala Val His Gln Val Phe Gly
 705 710 715 720
 Ser Val Tyr Thr Thr Met Phe Gly Gly Val Ser Trp Met Ile Arg Ile
 725 730 735
 Leu Ile Gly Phe Leu Val Leu Trp Ile Gly Thr Asn Ser Arg Asn Thr
 740 745 750
 Ser Met Ala Met Thr Cys Ile Ala Val Gly Gly Ile Thr Leu Phe Leu
 755 760 765
 Gly Phe Thr Val Gln Ala Asp Met Gly Cys Val Val Ser Trp Ser Gly
 770 775 780
 Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Val Val Asp Asn Val His
 785 790 795 800
 Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ala Arg Leu
 805 810 815
 Ala Ser Ala Ile Leu Asn Ala His Lys Asp Gly Val Cys Gly Ile Arg
 820 825 830
 Ser Thr Thr Arg Leu Glu Asn Val Met Trp Lys Gln Ile Thr Asn Glu
 835 840 845
 Leu Asn Tyr Val Leu Trp Glu Gly Gly His Asp Leu Thr Val Val Ala
 850 855 860

311

Gly	Asp	Val	Lys	Gly	Val	Leu	Thr	Lys	Gly	Lys	Arg	Ala	Leu	Thr	Pro	
865				870					875						880	
Pro	Val	Asn	Asp	Leu	Lys	Tyr	Ser	Trp	Lys	Thr	Trp	Gly	Lys	Ala	Lys	
				885					890						895	
Ile	Phe	Thr	Pro	Glu	Ala	Arg	Asn	Ser	Thr	Phe	Leu	Ile	Asp	Gly	Pro	
				900					905					910		
Asp	Thr	Ser	Glu	Cys	Pro	Asn	Glu	Arg	Arg	Ala	Trp	Asn	Phe	Leu	Glu	
				915					920					925		
Val	Glu	Asp	Tyr	Gly	Phe	Gly	Met	Phe	Thr	Thr	Asn	Ile	Trp	Met	Lys	
				930					935					940		
Phe	Arg	Glu	Gly	Ser	Ser	Glu	Val	Cys	Asp	His	Arg	Leu	Met	Ser	Ala	
				945					950					955		
Ala	Ile	Lys	Asp	Gln	Lys	Ala	Val	His	Ala	Asp	Met	Gly	Tyr	Trp	Ile	
				965					970					975		
Glu	Ser	Ser	Lys	Asn	Gln	Thr	Trp	Gln	Ile	Glu	Lys	Ala	Ser	Leu	Ile	
				980					985					990		
Glu	Val	Lys	Thr	Cys	Leu	Trp	Pro	Lys	Thr	His	Thr	Leu	Trp	Ser	Asn	
				995					1000					1005		
Gly	Val	Leu	Glu	Ser	Gln	Met	Leu	Ile	Pro	Lys	Ser	Tyr	Ala	Gly	Pro	
				1010					1015					1020		
Phe	Ser	His	His	Asn	Tyr	Arg	Gln	Gly	Tyr	Ala	Thr	Gln	Thr	Val	Gly	
				1025					1030					1035		
Pro	Trp	His	Leu	Gly	Lys	Leu	Glu	Ile	Asp	Phe	Gly	Glu	Cys	Pro	Gly	
				1045					1050					1055		
Thr	Thr	Val	Ala	Ile	Gln	Glu	Asp	Cys	Asp	His	Arg	Gly	Pro	Ser	Leu	
				1060					1065					1070		
Arg	Thr	Thr	Thr	Ala	Ser	Gly	Lys	Leu	Val	Thr	Gln	Trp	Cys	Cys	Arg	
				1075					1080					1085		
Ser	Cys	Thr	Met	Pro	Pro	Leu	Arg	Phe	Leu	Gly	Glu	Asp	Gly	Cys	Trp	
				1090					1095					1100		
Tyr	Gly	Met	Glu	Ile	Arg	Pro	Leu	Ser	Glu	Lys	Glu	Glu	Asn	Met	Val	
				1105					1110					1115		
Lys	Ser	Gln	Val	Thr	Ala	Gly	Gln	Gly	Thr	Ser	Glu	Thr	Phe	Ser	Met	
				1125					1130					1135		
Gly	Leu	Leu	Cys	Leu	Thr	Leu	Phe	Val	Glu	Glu	Cys	Leu	Arg	Arg	Arg	
				1140					1145					1150		
Val	Thr	Arg	Lys	His	Met	Ile	Leu	Val	Val	Val	Ile	Thr	Leu	Cys	Ala	
				1155					1160					1165		
Ile	Ile	Leu	Gly	Gly	Leu	Thr	Trp	Met	Asp	Leu	Leu	Arg	Ala	Leu	Ile	
				1170					1175					1180		
Met	Leu	Gly	Asp	Thr	Met	Ser	Gly	Arg	Ile	Gly	Gly	Gln	Ile	His	Leu	
				1185					1190					1195		
Ala	Ile	Met	Ala	Val	Phe	Lys	Met	Ser	Pro	Gly	Tyr	Val	Leu	Gly	Val	
				1205					1210					1215		
Phe	Leu	Arg	Lys	Leu	Thr	Ser	Arg	Glu	Thr	Ala	Leu	Met	Val	Ile	Gly	
				1220					1225					1230		
Met	Ala	Met	Thr	Thr	Val	Leu	Ser	Ile	Pro	His	Asp	Leu	Met	Glu	Leu	
				1235					1240					1245		
Ile	Asp	Gly	Ile	Ser	Leu	Gly	Leu	Ile	Leu	Leu	Lys	Ile	Val	Thr	His	
				1250					1255					1260		
Phe	Asp	Asn	Thr	Gln	Val	Gly	Thr	Leu	Ala	Leu	Ser	Leu	Thr	Phe	Ile	
				1265					1270					1275		
Arg	Ser	Thr	Met	Pro	Leu	Val	Met	Ala	Trp	Arg	Thr	Ile	Met	Ala	Val	
				1285					1290					1295		

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Leu Phe Val Val Thr Leu Ile Pro Leu Cys Arg Thr Ser Cys Leu Gln
 1300 1305 1310
 Lys Gln Ser His Trp Val Glu Ile Thr Ala Leu Ile Leu Gly Ala Gln
 1315 1320 1325
 Ala Leu Pro Val Tyr Leu Met Thr Leu Met Lys Gly Ala Ser Arg Arg
 1330 1335 1340
 Ser Trp Pro Leu Asn Glu Gly Ile Met Ala Val Gly Leu Val Ser Leu
 1345 1350 1355 1360
 Leu Gly Ser Ala Leu Leu Lys Asn Asp Val Pro Leu Ala Gly Pro Met
 1365 1370 1375
 Val Ala Gly Gly Leu Leu Leu Ala Ala Tyr Val Met Ser Gly Ser Ser
 1380 1385 1390
 Ala Asp Leu Ser Leu Glu Lys Ala Ala Asn Val Gln Trp Asp Glu Met
 1395 1400 1405
 Ala Asp Ile Thr Gly Ser Ser Pro Ile Ile Glu Val Lys Gln Asp Glu
 1410 1415 1420
 Asp Gly Ser Phe Ser Ile Arg Asp Val Glu Glu Thr Asn Met Ile Thr
 1425 1430 1435 1440
 Leu Leu Val Lys Leu Ala Leu Ile Thr Val Ser Gly Leu Tyr Pro Leu
 1445 1450 1455
 Ala Ile Pro Val Thr Met Thr Leu Trp Tyr Met Trp Gln Val Lys Thr
 1460 1465 1470
 Gln Arg Ser Gly Ala Leu Trp Asp Val Pro Ser Pro Ala Ala Thr Gln
 1475 1480 1485
 Lys Ala Ala Leu Ser Glu Gly Val Tyr Arg Ile Met Gln Arg Gly Leu
 1490 1495 1500
 Phe Gly Lys Thr Gln Val Gly Val Gly Ile His Met Glu Gly Val Phe
 1505 1510 1515 1520
 His Thr Met Trp His Val Thr Arg Gly Ser Val Ile Cys His Glu Thr
 1525 1530 1535
 Gly Arg Leu Glu Pro Ser Trp Ala Asp Val Arg Asn Asp Met Ile Ser
 1540 1545 1550
 Tyr Gly Gly Gly Trp Arg Leu Gly Asp Lys Trp Asp Lys Glu Glu Asp
 1555 1560 1565
 Val Gln Val Leu Ala Ile Glu Pro Gly Lys Asn Pro Lys His Val Gln
 1570 1575 1580
 Thr Lys Pro Gly Leu Phe Lys Thr Leu Thr Gly Glu Ile Gly Ala Val
 1585 1590 1595 1600
 Thr Leu Asp Phe Lys Pro Gly Thr Ser Gly Ser Pro Ile Ile Asn Arg
 1605 1610 1615
 Lys Gly Lys Val Ile Gly Leu Tyr Gly Asn Gly Val Val Thr Lys Ser
 1620 1625 1630
 Gly Asp Tyr Val Ser Ala Ile Thr Gln Ala Glu Arg Ile Gly Glu Pro
 1635 1640 1645
 Asp Tyr Glu Val Asp Glu Asp Ile Phe Arg Lys Lys Arg Leu Thr Ile
 1650 1655 1660
 Met Asp Leu His Pro Gly Ala Gly Lys Thr Lys Arg Ile Leu Pro Ser
 1665 1670 1675 1680
 Ile Val Arg Glu Ala Leu Lys Arg Arg Leu Arg Thr Leu Ile Leu Ala
 1685 1690 1695
 Pro Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly Leu
 1700 1705 1710
 Pro Ile Arg Tyr Gln Thr Pro Ala Val Lys Ser Glu His Thr Gly Arg
 1715 1720 1725

313

Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Thr Arg Leu Leu
 1730 1735 1740
 Ser Ser Thr Arg Val Pro Asn Tyr Asn Leu Ile Val Met Asp Glu Ala
 1745 1750 1755 1760
 His Phe Thr Asp Pro Ser Ser Val Ala Ala Arg Gly Tyr Ile Ser Thr
 1765 1770 1775
 Arg Val Glu Met Gly Glu Ala Ala Ala Ile Phe Met Thr Ala Thr Pro
 1780 1785 1790
 Pro Gly Ala Thr Asp Pro Phe Pro Gln Ser Asn Ser Pro Ile Glu Asp
 1795 1800 1805
 Ile Glu Arg Glu Ile Pro Glu Arg Ser Trp Asn Thr Gly Phe Asp Trp
 1810 1815 1820
 Ile Thr Asp Tyr Gln Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys
 1825 1830 1835
 Ala Gly Asn Asp Ile Ala Asn Cys Leu Arg Lys Ser Gly Lys Lys Val
 1845 1850 1855
 Ile Gln Leu Ser Arg Lys Thr Phe Asp Thr Glu Tyr Pro Lys Thr Lys
 1860 1865 1870
 Leu Thr Asp Trp Asp Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly
 1875 1880 1885
 Ala Asn Phe Arg Ala Gly Arg Val Ile Asp Pro Arg Arg Cys Leu Lys
 1890 1895 1900
 Pro Val Ile Leu Thr Asp Gly Pro Glu Arg Val Ile Leu Ala Gly Pro
 1905 1910 1915
 Ile Pro Val Thr Pro Ala Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly
 1925 1930 1935
 Arg Asn Pro Ala Gln Glu Asp Asp Gln Tyr Val Phe Ser Gly Asp Pro
 1940 1945 1950
 Leu Lys Asn Asp Glu Asp His Ala His Trp Thr Glu Ala Lys Met Leu
 1955 1960 1965
 Leu Asp Asn Ile Tyr Thr Pro Glu Gly Ile Ile Pro Thr Leu Phe Gly
 1970 1975 1980
 Pro Glu Arg Glu Lys Thr Gln Ala Ile Asp Gly Glu Phe Arg Leu Arg
 1985 1990 1995 2000
 Gly Glu Gln Arg Lys Thr Phe Val Glu Leu Met Arg Arg Gly Asp Leu
 2005 2010 2015
 Pro Val Trp Leu Ser Tyr Lys Val Ala Ser Ala Gly Ile Ser Tyr Lys
 2020 2025 2030
 Asp Arg Glu Trp Cys Phe Thr Gly Glu Arg Asn Asn Gln Ile Leu Glu
 2035 2040 2045
 Glu Asn Met Glu Val Glu Ile Trp Thr Arg Glu Gly Glu Lys Lys Lys
 2050 2055 2060
 Leu Arg Pro Arg Trp Leu Asp Ala Arg Val Tyr Ala Asp Pro Met Ala
 2065 2070 2075 2080
 Leu Lys Asp Phe Lys Glu Phe Ala Ser Gly Arg Lys Ser Ile Thr Leu
 2085 2090 2095
 Asp Ile Leu Thr Glu Ile Ala Ser Leu Pro Thr Tyr Leu Ser Ser Arg
 2100 2105 2110
 Ala Lys Leu Ala Leu Asp Asn Ile Val Met Leu His Thr Thr Glu Arg
 2115 2120 2125
 Gly Gly Arg Ala Tyr Gln His Ala Leu Asn Glu Leu Pro Glu Ser Leu
 2130 2135 2140
 Glu Thr Leu Met Leu Val Ala Leu Leu Gly Ala Met Thr Ala Gly Ile
 2145 2150 2155 2160

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Phe	Leu	Phe	Phe	Met	Gln	Gly	Lys	Gly	Ile	Gly	Lys	Leu	Ser	Met	Gly
				2165					2170						2175
Leu	Ile	Thr	Ile	Ala	Val	Ala	Ser	Gly	Leu	Phe	Trp	Val	Ala	Glu	Ile
			2180					2185					2190		
Gln	Pro	Gln	Trp	Ile	Ala	Ala	Ser	Ile	Ile	Leu	Glu	Phe	Phe	Leu	Met
			2195				2200					2205			
Val	Leu	Leu	Ile	Pro	Glu	Pro	Glu	Lys	Gln	Arg	Thr	Pro	Gln	Asp	Asn
			2210				2215				2220				
Gln	Leu	Ile	Tyr	Val	Ile	Leu	Thr	Ile	Leu	Thr	Ile	Ile	Gly	Leu	Ile
			2225			2230			2235						2240
Ala	Ala	Asn	Glu	Met	Gly	Leu	Ile	Glu	Lys	Thr	Lys	Thr	Asp	Phe	Gly
			2245						2250					2255	
Phe	Tyr	Gln	Val	Lys	Thr	Glu	Thr	Ile	Leu	Asp	Val	Asp	Leu	Arg	
			2260				2265					2270			
Pro	Ala	Ser	Ala	Trp	Thr	Leu	Tyr	Ala	Val	Ala	Thr	Thr	Phe	Leu	Thr
			2275				2280					2285			
Pro	Met	Leu	Arg	His	Thr	Ile	Glu	Asn	Thr	Ser	Ala	Asn	Leu	Ser	Leu
			2290			2295				2300					
Ala	Ala	Ile	Ala	Asn	Gln	Ala	Ala	Val	Leu	Met	Gly	Leu	Gly	Lys	Gly
			2305		2310				2315						2320
Trp	Pro	Leu	His	Arg	Met	Asp	Leu	Gly	Val	Pro	Leu	Leu	Ala	Met	Gly
			2325					2330					2335		
Cys	Tyr	Ser	Gln	Val	Asn	Pro	Thr	Thr	Leu	Thr	Ala	Ser	Leu	Val	Met
			2340					2345					2350		
Leu	Ser	Val	His	Tyr	Ala	Ile	Ile	Gly	Pro	Gly	Leu	Gln	Ala	Lys	Ala
			2355				2360				2365				
Thr	Arg	Glu	Ala	Gln	Lys	Arg	Thr	Ala	Ala	Gly	Ile	Met	Lys	Asn	Pro
			2370				2375				2380				
Thr	Val	Asp	Gly	Ile	Thr	Val	Ile	Asp	Leu	Glu	Pro	Ile	Ser	Tyr	Asp
			2385		2390			2395					2400		
Pro	Lys	Phe	Glu	Lys	Gln	Leu	Gly	Gln	Val	Met	Leu	Leu	Val	Leu	Cys
			2405					2410					2415		
Ala	Gly	Gln	Leu	Leu	Leu	Met	Arg	Thr	Thr	Trp	Ala	Phe	Cys	Glu	Val
			2420					2425				2430			
Leu	Thr	Leu	Ala	Thr	Gly	Pro	Ile	Leu	Thr	Leu	Trp	Glu	Gly	Asn	Pro
			2435			2440					2445				
Gly	Arg	Phe	Trp	Asn	Thr	Thr	Ile	Ala	Val	Ser	Thr	Ala	Asn	Ile	Phe
			2450		2455					2460					
Arg	Gly	Ser	Tyr	Leu	Ala	Gly	Ala	Gly	Leu	Ala	Phe	Ser	Leu	Ile	Lys
			2465		2470			2475							2480
Asn	Val	Gln	Thr	Pro	Arg	Arg	Gly	Thr	Gly	Thr	Thr	Gly	Glu	Thr	Leu
			2485					2490					2495		
Gly	Glu	Lys	Trp	Lys	Arg	Gln	Leu	Asn	Ser	Leu	Tyr	Arg	Lys	Glu	Phe
			2500												

315

Gly Gly Pro Gly His Glu Glu Pro Ile Pro Met Ala Thr Tyr Gly Trp
 2595 2600 2605
 Asn Leu Val Lys Leu His Ser Gly Val Asp Val Phe Tyr Lys Pro Thr
 2610 2615 2620
 Glu Gln Val Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Ser Asn
 2625 2630 2635 2640
 Pro Thr Ile Glu Glu Gly Arg Thr Leu Arg Val Leu Lys Met Val Glu
 2645 2650 2655
 Pro Trp Leu Ser Ser Lys Pro Glu Phe Cys Ile Lys Val Leu Asn Pro
 2660 2665 2670
 Tyr Met Pro Thr Val Ile Glu Glu Leu Glu Lys Leu Gln Arg Lys His
 2675 2680 2685
 Gly Gly Asn Leu Val Arg Cys Pro Leu Ser Arg Asn Ser Thr His Glu
 2690 2695 2700
 Met Tyr Trp Val Ser Gly Ala Ser Gly Asn Ile Val Ser Ser Val Asn
 2705 2710 2715 2720
 Thr Thr Ser Lys Met Leu Leu Asn Arg Phe Thr Thr Arg His Arg Lys
 2725 2730 2735
 Pro Thr Tyr Glu Lys Asp Val Asp Leu Gly Ala Gly Thr Arg Ser Val
 2740 2745 2750
 Ser Thr Glu Thr Glu Lys Pro Asp Met Thr Ile Ile Gly Arg Arg Leu
 2755 2760 2765
 Gln Arg Leu Gln Glu Glu His Lys Glu Thr Trp His Tyr Asp Gln Glu
 2770 2775 2780
 Asn Pro Tyr Arg Thr Trp Ala Tyr His Gly Ser Tyr Glu Ala Pro Ser
 2785 2790 2795 2800
 Thr Gly Ser Ala Ser Ser Met Val Asn Gly Val Val Lys Leu Leu Thr
 2805 2810 2815
 Lys Pro Trp Asp Val Val Pro Met Val Thr Gln Leu Ala Met Thr Asp
 2820 2825 2830
 Thr Thr Pro Phe Gly Gln Gln Arg Val Phe Lys Glu Lys Val Asp Thr
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 Cys Thr Arg Glu Glu Phe Ile Ser Lys Val Arg Ser Asn Ala Ala Ile
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 Val Asn Asp Ser Arg Phe Trp Glu Leu Val Asp Lys Glu Arg Ala Leu
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 His Gln Glu Gly Lys Cys Glu Ser Cys Val Tyr Asn Met Met Gly Lys
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 Arg Glu Lys Lys Leu Gly Glu Phe Gly Arg Ala Lys Gly Ser Arg Ala
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 Ile Trp Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu Phe Glu Ala Leu
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 Gly Phe Leu Asn Glu Asp His Trp Phe Gly Arg Glu Asn Ser Trp Ser
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 Gly Val Glu Gly Glu Gly Leu His Arg Leu Gly Tyr Ile Leu Glu Glu
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 Ile Asp Lys Lys Asp Gly Asp Leu Met Tyr Ala Asp Asp Thr Ala Gly
 3010 3015 3020

316

Trp Asp Thr Arg Ile Thr Glu Asp Asp Leu Gln Asn Glu Glu Leu Ile
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 Thr Glu Gln Met Ala Pro His His Lys Ile Leu Ala Lys Ala Ile Phe
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 Lys Leu Thr Tyr Gln Asn Lys Val Val Lys Val Leu Arg Pro Thr Pro
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 Arg Gly Ala Val Met Asp Ile Ile Ser Arg Lys Asp Gln Arg Gly Ser
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<213> Artificial Sequence

<220>

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 synthetic construct

317

<221> CDS

<222> (97)...(10272)

<400> 27

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                               Met Asn Asn Gln Arg Lys
                               1                               5

aag gcg aaa aac acg cct ttc aat atg ctg aaa cgc gag aga aac cgc      162
Lys Ala Lys Asn Thr Pro Phe Asn Met Leu Lys Arg Glu Arg Asn Arg
                               10                               15                               20

gtg tcg act gtg caa cag ctg aca aag aga ttc tca ctt gga atg ctg      210
Val Ser Thr Val Gln Gln Leu Thr Lys Arg Phe Ser Leu Gly Met Leu
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cag gga cga gga cca tta aaa ctg ttc atg gcc ctg gtg gcg ttc ctt      258
Gln Gly Arg Gly Pro Leu Lys Leu Phe Met Ala Leu Val Ala Phe Leu
                               40                               45                               50

cgt ttc cta aca atc cca cca aca gca ggg ata ttg aag aga tgg gga      306
Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly Ile Leu Lys Arg Trp Gly
                               55                               60                               65                               70

aca att aaa aaa tca aaa gct att aat gtt ttg aga ggg ttc agg aaa      354
Thr Ile Lys Lys Ser Lys Ala Ile Asn Val Leu Arg Gly Phe Arg Lys
                               75                               80                               85

gag att gga agg atg ctg aac atc ttg aat agg aga cgc aga tct gca      402
Glu Ile Gly Arg Met Leu Asn Ile Leu Asn Arg Arg Arg Ser Ala
                               90                               95                               100

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Gly Met Ile Ile Met Leu Ile Pro Thr Val Met Ala Phe His Leu Thr
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acg cgt ggg gga gag ccg cat atg ata gtt agc aag cag gaa aga gga      498
Thr Arg Gly Gly Glu Pro His Met Ile Val Ser Lys Gln Glu Arg Gly
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aag tca ctt ttg ttc aag acc tct gca ggt gtc aac atg tgc acc ctc      546
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Ile Ala Met Asp Leu Gly Glu Leu Cys Glu Asp Thr Met Thr Tyr Lys
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tgc ccc cgg atc act gag gcg gaa cca gat gac gtt gac tgt tgg tgc      642
Cys Pro Arg Ile Thr Glu Ala Glu Pro Asp Asp Val Asp Cys Trp Cys
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318

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Glu His Arg Arg Asp Lys Arg Ser Val Ala Leu Ala Pro His Val Gly	
200 205 210	
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Leu Gly Leu Glu Thr Arg Ala Glu Thr Trp Met Ser Ser Glu Gly Ala	
215 220 225 230	
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Trp Lys Gln Ile Gln Lys Val Glu Thr Trp Ala Leu Arg His Pro Gly	
235 240 245	
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Phe Thr Val Ile Ala Leu Phe Leu Ala His Ala Ile Gly Thr Ser Ile	
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Thr Gln Lys Gly Ile Ile Phe Ile Leu Leu Met Leu Val Thr Pro Ser	
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Met Ala Met Arg Cys Val Gly Ile Gly Asn Arg Asp Phe Val Glu Gly	
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Leu Ser Gly Ala Thr Trp Val Asp Val Val Leu Glu His Gly Ser Cys	
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Val Thr Thr Met Ala Lys Asn Lys Pro Thr Leu Asp Ile Glu Leu Leu	
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Ala Lys Ile Ser Asn Thr Thr Thr Asp Ser Arg Cys Pro Thr Gln Gly	
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Glu Ala Thr Leu Val Glu Glu Gln Asp Ala Asn Phe Val Cys Arg Arg	
360 365 370	
acg ttc gtg gac aga ggc tgg ggc aat ggc tgt ggg cta ttc gga aaa	1266
Thr Phe Val Asp Arg Gly Trp Gly Asn Gly Cys Gly Leu Phe Gly Lys	
375 380 385 390	
ggt agt cta ata acg tgt gcc aag ttt aag tgt gtg aca aaa cta gaa	1314
Gly Ser Leu Ile Thr Cys Ala Lys Phe Lys Cys Val Thr Lys Leu Glu	
395 400 405	

319

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320

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322

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323

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324

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325

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gag gca gct ggg att ttt atg aca gcc act ccc ccg gga agc aga gac Glu Ala Ala Gly Ile Phe Met Thr Ala Thr Pro Pro Gly Ser Arg Asp 1785 1790 1795	5490
cca ttt cct cag agc aat gca cca atc ata gat gaa gaa aga gaa atc Pro Phe Pro Gln Ser Asn Ala Pro Ile Ile Asp Glu Glu Arg Glu Ile 1800 1805 1810	5538
cct gaa cgc tcg tgg aat tcc gga cat gaa tgg gtc acg gat ttt aaa Pro Glu Arg Ser Trp Asn Ser Gly His Glu Trp Val Thr Asp Phe Lys 1815 1820 1825 1830	5586
ggg aag act gtt tgg ttc gtt cca agt ata aaa gca gga aat gat ata Gly Lys Thr Val Trp Phe Val Pro Ser Ile Lys Ala Gly Asn Asp Ile 1835 1840 1845	5634
gca gct tgc ctg agg aaa aat gga aag aaa gtg ata caa ctc agt agg Ala Ala Cys Leu Arg Lys Asn Gly Lys Lys Val Ile Gln Leu Ser Arg 1850 1855 1860	5682
aag acc ttt gat tct gag tat gtc aag act aga acc aat gat tgg gac Lys Thr Phe Asp Ser Glu Tyr Val Lys Thr Arg Thr Asn Asp Trp Asp 1865 1870 1875	5730
ttc gtg gtt aca act gac att tca gaa atg ggt gcc aat ttc aag gct Phe Val Val Thr Thr Asp Ile Ser Glu Met Gly Ala Asn Phe Lys Ala 1880 1885 1890	5778
gag agg gtt ata gac ccc aga cgc tgc atg aaa cca gtc ata cta aca Glu Arg Val Ile Asp Pro Arg Arg Cys Met Lys Pro Val Ile Leu Thr 1895 1900 1905 1910	5826

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gat ggt gaa gag cgg gtg att ctg gca gga cct atg cca gtg acc cac Asp Gly Glu Glu Arg Val Ile Leu Ala Gly Pro Met Pro Val Thr His 1915 1920 1925	5874
tct agt gca gca caa aga aga ggg aga ata gga aga aat cca aaa aat Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile Gly Arg Asn Pro Lys Asn 1930 1935 1940	5922
gag aat gac cag tac ata tac atg ggg gaa cct ctg gaa aat gat gaa Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu Pro Leu Glu Asn Asp Glu 1945 1950 1955	5970
gac tgt gca cac tgg aaa gaa gct aaa atg ctc cta gat aac atc aac Asp Cys Ala His Trp Lys Glu Ala Lys Met Leu Leu Asp Asn Ile Asn 1960 1965 1970	6018
acg cca gaa gga atc att cct agc atg ttc gaa cca gag cgt gaa aag Thr Pro Glu Gly Ile Ile Pro Ser Met Phe Glu Pro Glu Arg Glu Lys 1975 1980 1985 1990	6066
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acc ttt gta gac tta atg aga aga gga gac cta cca gtc tgg ttg gcc Thr Phe Val Asp Leu Met Arg Arg Gly Asp Leu Pro Val Trp Leu Ala 2010 2015 2020	6162
tac aga gtg gca gct gaa ggc atc aac tac gca gac aga agg tgg tgt Tyr Arg Val Ala Ala Glu Gly Ile Asn Tyr Ala Asp Arg Arg Trp Cys 2025 2030 2035	6210
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gaa atc tgg aca aaa gaa ggg gaa agg aag aaa ttg aaa ccc aga tgg Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys Lys Leu Lys Pro Arg Trp 2055 2060 2065 2070	6306
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gaa ttt gca gcc gga aga aag tct ctg acc ctg aac cta atc aca gaa Glu Phe Ala Ala Gly Arg Lys Ser Leu Thr Leu Asn Leu Ile Thr Glu 2090 2095 2100	6402
atg ggt agg ctc cca acc ttc atg act cag aag gca aga gac gca ctg Met Gly Arg Leu Pro Thr Phe Met Thr Gln Lys Ala Arg Asp Ala Leu 2105 2110 2115	6450
gac aac tta gca gtg ctg cac acg gct gag gca ggt gga agg gcg tac Asp Asn Leu Ala Val Leu His Thr Ala Glu Ala Gly Gly Arg Ala Tyr 2120 2125 2130	6498

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aac cat gct ctc agt gaa ctg ccg gag acc ctg gag aca ttg ctt tta Asn His Ala Leu Ser Glu Leu Pro Glu Thr Leu Glu Thr Leu Leu Leu 2135 2140 2145 2150	6546
ctg aca ctt ctg gct aca gtc acg gga ggg atc ttt tta ttc ttg atg Leu Thr Leu Leu Ala Thr Val Thr Gly Gly Ile Phe Leu Phe Leu Met 2155 2160 2165	6594
agc gca agg ggc ata ggg aag atg acc ctg gga atg tgc tgc ata atc Ser Ala Arg Gly Ile Gly Lys Met Thr Leu Gly Met Cys Ile Ile 2170 2175 2180	6642
acg gct agc atc ctc cta tgg tac gca caa ata cag cca cac tgg ata Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln Ile Gln Pro His Trp Ile 2185 2190 2195	6690
gca gct tca ata ata ctg gag ttt ttt ctc ata gtt ttg ctt att cca Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu Ile Val Leu Leu Ile Pro 2200 2205 2210	6738
gaa cct gaa aaa cag aga aca ccc caa gac aac caa ctg acc tac gtt Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp Asn Gln Leu Thr Tyr Val 2215 2220 2225 2230	6786
gtc ata gcc atc ctc aca gtg gtg gcc gca acc atg gca aac gag atg Val Ile Ala Ile Leu Thr Val Val Ala Ala Thr Met Ala Asn Glu Met 2235 2240 2245	6834
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acc cag caa ccc gag agc aac atc ctg gac ata gat cta cgt cct gca Thr Gln Gln Pro Glu Ser Asn Ile Leu Asp Ile Asp Leu Arg Pro Ala 2265 2270 2275	6930
tca gca tgg acg ctg tat gcc gtg gcc aca aca ttt gtt aca cca atg Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr Thr Phe Val Thr Pro Met 2280 2285 2290	6978
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ata gcc aac caa gcc aca gtg tta atg ggt ctc ggg aaa gga tgg cca Ile Ala Asn Gln Ala Thr Val Leu Met Gly Leu Gly Lys Gly Trp Pro 2315 2320 2325	7074
ttg tca aag atg gac atc gga gtt ccc ctt ctc gcc att gga tgc tac Leu Ser Lys Met Asp Ile Gly Val Pro Leu Leu Ala Ile Gly Cys Tyr 2330 2335 2340	7122

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tca caa gtc aac ccc ata act ctc aca gca gct ctt ttc tta ttg gta	7170
Ser Gln Val Asn Pro Ile Thr Leu Thr Ala Ala Leu Phe Leu Leu Val	
2345 2350 2355	
gca cat tat gcc atc ata ggg cca gga ctc caa gca aaa gca acc aga	7218
Ala His Tyr Ala Ile Ile Gly Pro Gly Leu Gln Ala Lys Ala Thr Arg	
2360 2365 2370	
gaa gct cag aaa aga gca gcg gcg ggc atc atg aaa aac cca act gtc	7266
Glu Ala Gln Lys Arg Ala Ala Ala Gly Ile Met Lys Asn Pro Thr Val	
2375 2380 2385 2390	
gat gga ata aca gtg att gac cta gat cca ata cct tat gat cca aag	7314
Asp Gly Ile Thr Val Ile Asp Leu Asp Pro Ile Pro Tyr Asp Pro Lys	
2395 2400 2405	
ttt gaa aag cag ttg gga caa gta atg ctc cta gtc ctc tgc gtg act	7362
Phe Glu Lys Gln Leu Gly Gln Val Met Leu Leu Val Leu Cys Val Thr	
2410 2415 2420	
caa gta ttg atg atg agg act aca tgg gct ctg tgt gag gct tta acc	7410
Gln Val Leu Met Met Arg Thr Thr Trp Ala Leu Cys Glu Ala Leu Thr	
2425 2430 2435	
tta gct acc ggg ccc atc tcc aca ttg tgg gaa gga aat cca ggg agg	7458
Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp Glu Gly Asn Pro Gly Arg	
2440 2445 2450	
ttt tgg aac act acc att gcg gtg tca atg gct aac att ttt aga ggg	7506
Phe Trp Asn Thr Thr Ile Ala Val Ser Met Ala Asn Ile Phe Arg Gly	
2455 2460 2465 2470	
agt tac ttg gcc gga gct gga ctt ctc ttt tct att atg aag aac aca	7554
Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe Ser Ile Met Lys Asn Thr	
2475 2480 2485	
acc aac aca aga agg gga act ggc aac ata gga gag acg ctt gga gag	7602
Thr Asn Thr Arg Arg Gly Thr Gly Asn Ile Gly Glu Thr Leu Gly Glu	
2490 2495 2500	
aaa tgg aaa agc cga ttg aac gca ttg gga aaa agt gaa ttc cag atc	7650
Lys Trp Lys Ser Arg Leu Asn Ala Leu Gly Lys Ser Glu Phe Gln Ile	
2505 2510 2515	
tac aag aaa agt gga atc cag gaa gtg gat aga acc tta gca aaa gaa	7698
Tyr Lys Lys Ser Gly Ile Gln Glu Val Asp Arg Thr Leu Ala Lys Glu	
2520 2525 2530	
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Gly Ile Lys Arg Gly Glu Thr Asp His His Ala Val Ser Arg Gly Ser	
2535 2540 2545 2550	
gca aaa ctg aga tgg ttc gtt gag aga aac atg gtc aca cca gaa ggg	7794
Ala Lys Leu Arg Trp Phe Val Glu Arg Asn Met Val Thr Pro Glu Gly	
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cca gga cac gaa gaa ccc atc ccc atg tca aca tat ggg tgg aat cta Pro Gly His Glu Glu Pro Ile Pro Met Ser Thr Tyr Gly Trp Asn Leu 2600 2605 2610	7938
gtg cgt ctt caa agt gga gtt gac gtt ttc ttc atc ccg cca gaa aag Val Arg Leu Gln Ser Gly Val Asp Val Phe Phe Ile Pro Pro Glu Lys 2615 2620 2625 2630	7986
tgt gac aca tta ttg tgt gac ata ggg gag tca tca cca aat ccc aca Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu Ser Ser Pro Asn Pro Thr 2635 2640 2645	8034
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ccc tca gtc ata gaa aaa atg gaa gca cta caa agg aaa tat gga gga Pro Ser Val Ile Glu Lys Met Glu Ala Leu Gln Arg Lys Tyr Gly Gly 2680 2685 2690	8178
gcc tta gtg agg aat cca ctc tca cga aac tcc aca cat gag atg tac Ala Leu Val Arg Asn Pro Leu Ser Arg Asn Ser Thr His Glu Met Tyr 2695 2700 2705 2710	8226
tgg gta tcc aat gct tcc ggg aac ata gtg tca tca gtg aac atg att Trp Val Ser Asn Ala Ser Gly Asn Ile Val Ser Ser Val Asn Met Ile 2715 2720 2725	8274
tca agg atg ttg atc aac aga ttt aca atg aga tac aag aya gcc act Ser Arg Met Leu Ile Asn Arg Phe Thr Met Arg Tyr Lys Lys Ala Thr 2730 2735 2740	8322
tac gag ccg gat gtt gac ctc gga agc gga acc cgt aac atc ggg att Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly Thr Arg Asn Ile Gly Ile 2745 2750 2755	8370
gaa agt gag ata cca aac cta gat ata att ggg aaa aga ata gaa aaa Glu Ser Glu Ile Pro Asn Leu Asp Ile Ile Gly Lys Arg Ile Glu Lys 2760 2765 2770	8418

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ata aag caa gag cat gaa aca tca tgg cac tat gac caa gac cac cca ile Lys Gln Glu His Glu Thr Ser Trp His Tyr Asp Gln Asp His Pro 2775 2780 2785 2790	8466
tac aaa acg tgg gca tac cat ggt agc tat gaa aca aaa cag act gga Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr Glu Thr Lys Gln Thr Gly 2795 2800 2805	8514
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gat agt agg ttt tgg gag ctg gtt gac aag gaa agg aat ctc cat ctt Asp Ser Arg Phe Trp Glu Leu Val Asp Lys Glu Arg Asn Leu His Leu 2920 2925 2930	8898
gaa gga aag tgt gaa aca tgt gtg tac aac atg atg gga aaa aga gag Glu Gly Lys Cys Glu Thr Cys Val Tyr Asn Met Met Gly Lys Arg Glu 2935 2940 2945 2950	8946
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tac atg tgg ctt gga gca cgc ttc tta gag ttt gaa gcc cta gga ttc Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu Phe Glu Ala Leu Gly Phe 2970 2975 2980	9042
tta aat gaa gat cac tgg ttc tcc aga gag aac tcc ctg agt gga gtg Leu Asn Glu Asp His Trp Phe Ser Arg Glu Asn Ser Leu Ser Gly Val 2985 2990 2995	9090

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gaa gga gaa ggg ctg cac aag cta ggt tac att cta aga gac gtg agc Glu Gly Glu Gly Leu His Lys Leu Gly Tyr Ile Leu Arg Asp Val Ser 3000 3005 3010	9138
aag aaa gag gga gga gca atg tat gcc gat gac acc gca gga tgg gat Lys Lys Glu Gly Gly Ala Met Tyr Ala Asp Asp Thr Ala Gly Trp Asp 3015 3020 3025 3030	9186
aca aga atc aca cta gaa gac cta aaa aat gaa gaa atg gta aca aac Thr Arg Ile Thr Leu Glu Asp Leu Lys Asn Glu Glu Met Val Thr Asn 3035 3040 3045	9234
cac atg gaa gga gaa cac aag aaa cta gcc gag gcc att ttc aaa cta His Met Glu Gly Glu His Lys Lys Leu Ala Glu Ala Ile Phe Lys Leu 3050 3055 3060	9282
acg tac caa aac aag gtg gtg cgt gtg caa aga cca aca cca aga ggc Thr Tyr Gln Asn Lys Val Val Arg Val Gln Arg Pro Thr Pro Arg Gly 3065 3070 3075	9330
aca gta atg gac atc ata tcg aga aga gac caa aga ggt agt gga caa Thr Val Met Asp Ile Ile Ser Arg Arg Asp Gln Arg Gly Ser Gly Gln 3080 3085 3090	9378
gtt ggc acc tat gga ctc aat act ttc acc aat atg gaa gcc caa cta Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr Asn Met Glu Ala Gln Leu 3095 3100 3105 3110	9426
atc aga cag atg gag gga gaa gga gtc ttt aaa agc att cag cac cta Ile Arg Gln Met Glu Gly Glu Gly Val Phe Lys Ser Ile Gln His Leu 3115 3120 3125	9474
aca atc aca gaa gaa atc gct gtg caa aac tgg tta gca aga gtg ggg Thr Ile Thr Glu Glu Ile Ala Val Gln Asn Trp Leu Ala Arg Val Gly 3130 3135 3140	9522
cgc gaa agg tta tca aga atg gcc atc agt gga gat gat tgt gtt gtg Arg Glu Arg Leu Ser Arg Met Ala Ile Ser Gly Asp Asp Cys Val Val 3145 3150 3155	9570
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atg gga aag att agg aaa gac ata caa caa tgg gaa cct tca aga gga Met Gly Lys Ile Arg Lys Asp Ile Gln Gln Trp Glu Pro Ser Arg Gly 3175 3180 3185 3190	9666
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332

tta atc atg aaa gac ggt cgc gta ctc gtt gtt cca tgt aga aac caa Leu Ile Met Lys Asp Gly Arg Val Leu Val Val Pro Cys Arg Asn Gln 3210 3215 3220	9762
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gac caa tgg tgc ggc tca ttg att ggg tta aca agc agg gcc acc tgg Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu Thr Ser Arg Ala Thr Trp 3335 3340 3345 3350	10146
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gaa gag gaa gaa gca gga gtt ctg tgg tag aaagcaaaac taacatgaaa Glu Glu Glu Glu Ala Gly Val Leu Trp * 3385 3390	10292
caaggctaga agtcaggctg gattaagcca tagtacggaa aaaactatgc tacctgtgag cccgcgccaa ggagcttaaa agaagtcagg ccatcataaa tgccatagct tgagtaaact atgcagcctg tagctccacc tgagaagggt taaaaaatcc gggaggccac aaaccatgga agctgtacgc atggcgtagt ggactagcgg ttagaggaga cccctccctt acaaatcgca gcaacaatgg gggcccaagg cgagatgaag ctgtagtctc gctggaagga cttagaggta gaggagacc ccccgaaaca aaaaacagca tattgacgct gggaaagacc agagatcctg ctgtctctc agcatcatc caggcacaga acgccagaaa atggaatggt gctgttgat	10352 10412 10472 10532 10592 10652 10712

333

caacagggttc t

10723

<210> 28

<211> 3391

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<400> 28

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Lys Arg Glu Arg Asn Arg Val Ser Thr Val Gln Gln Leu Thr Lys Arg
      20           25           30
Phe Ser Leu Gly Met Leu Gln Gly Arg Gly Pro Leu Lys Leu Phe Met
      35           40           45
Ala Leu Val Ala Phe Leu Arg Phe Leu Thr Ile Pro Pro Thr Ala Gly
      50           55           60
Ile Leu Lys Arg Trp Gly Thr Ile Lys Lys Ser Lys Ala Ile Asn Val
65           70           75           80
Leu Arg Gly Phe Arg Lys Glu Ile Gly Arg Met Leu Asn Ile Leu Asn
      85           90           95
Arg Arg Arg Arg Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val
      100          105          110
Met Ala Phe His Leu Thr Thr Arg Gly Gly Glu Pro His Met Ile Val
      115          120          125
Ser Lys Gln Glu Arg Gly Lys Ser Leu Leu Phe Lys Thr Ser Ala Gly
      130          135          140
Val Asn Met Cys Thr Leu Ile Ala Met Asp Leu Gly Glu Leu Cys Glu
145          150          155          160
Asp Thr Met Thr Tyr Lys Cys Pro Arg Ile Thr Glu Ala Glu Pro Asp
      165          170          175
Asp Val Asp Cys Trp Cys Asn Ala Thr Asp Thr Trp Val Thr Tyr Gly
      180          185          190
Thr Cys Ser Gln Thr Gly Glu His Arg Arg Asp Lys Arg Ser Val Ala
      195          200          205
Leu Ala Pro His Val Gly Leu Gly Leu Glu Thr Arg Ala Glu Thr Trp
      210          215          220
Met Ser Ser Glu Gly Ala Trp Lys Gln Ile Gln Lys Val Glu Thr Trp
225          230          235          240
Ala Leu Arg His Pro Gly Phe Thr Val Ile Ala Leu Phe Leu Ala His
      245          250          255
Ala Ile Gly Thr Ser Ile Thr Gln Lys Gly Ile Ile Phe Ile Leu Leu
      260          265          270
Met Leu Val Thr Pro Ser Met Ala Met Arg Cys Val Gly Ile Gly Asn
      275          280          285
Arg Asp Phe Val Glu Gly Leu Ser Gly Ala Thr Trp Val Asp Val Val
      290          295          300
Leu Glu His Gly Ser Cys Val Thr Thr Met Ala Lys Asn Lys Pro Thr
305          310          315          320
Leu Asp Ile Glu Leu Leu Lys Thr Glu Val Thr Asn Pro Ala Val Leu
      325          330          335

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Arg Lys Leu Cys Ile Glu Ala Lys Ile Ser Asn Thr Thr Thr Asp Ser
 340 345 350
 Arg Cys Pro Thr Gln Gly Glu Ala Thr Leu Val Glu Glu Gln Asp Ala
 355 360 365
 Asn Phe Val Cys Arg Arg Thr Phe Val Asp Arg Gly Trp Gly Asn Gly
 370 375 380
 Cys Gly Leu Phe Gly Lys Gly Ser Leu Ile Thr Cys Ala Lys Phe Lys
 385 390 395 400
 Cys Val Thr Lys Leu Glu Gly Lys Ile Val Gln Tyr Glu Asn Leu Lys
 405 410 415
 Tyr Ser Val Ile Val Thr Val His Thr Gly Asp Gln His Gln Val Gly
 420 425 430
 Asn Glu Thr Thr Glu His Gly Thr Thr Ala Thr Ile Thr Pro Gln Ala
 435 440 445
 Pro Thr Ser Glu Ile Gln Leu Thr Asp Tyr Gly Thr Leu Thr Leu Asp
 450 455 460
 Cys Ser Pro Arg Thr Gly Leu Asp Phe Asn Glu Met Val Leu Leu Thr
 465 470 475 480
 Met Lys Glu Arg Ser Trp Leu Val His Lys Gln Trp Phe Leu Asp Leu
 485 490 495
 Pro Leu Pro Trp Thr Ser Gly Ala Ser Thr Ser Gln Glu Thr Trp Asn
 500 505 510
 Arg Gln Asp Leu Leu Val Thr Phe Lys Thr Ala His Ala Lys Lys Gln
 515 520 525
 Glu Val Val Val Leu Gly Ser Gln Glu Gly Ala Met His Thr Ala Leu
 530 535 540
 Thr Gly Ala Thr Glu Ile Gln Thr Ser Gly Thr Thr Thr Ile Phe Ala
 545 550 555 560
 Gly His Leu Lys Cys Arg Leu Lys Met Asp Lys Leu Thr Leu Lys Gly
 565 570 575
 Met Ser Tyr Val Met Cys Thr Gly Ser Phe Lys Leu Glu Lys Glu Val
 580 585 590
 Ala Glu Thr Gln His Gly Thr Val Leu Val Gln Val Lys Tyr Glu Gly
 595 600 605
 Thr Asp Ala Pro Cys Lys Ile Pro Phe Ser Thr Gln Asp Glu Lys Gly
 610 615 620
 Ala Thr Gln Asn Gly Arg Leu Ile Thr Ala Asn Pro Ile Val Thr Asp
 625 630 635 640
 Lys Glu Lys Pro Val Asn Ile Glu Ala Glu Pro Pro Phe Gly Glu Ser
 645 650 655
 Tyr Ile Val Val Gly Ala Gly Glu Lys Ala Leu Lys Leu Ser Trp Phe
 660 665 670
 Lys Lys Gly Ser Ser Ile Gly Lys Met Phe Glu Ala Thr Ala Arg Gly
 675 680 685
 Ala Arg Arg Met Ala Ile Leu Gly Asp Thr Ala Trp Asp Phe Gly Ser
 690 695 700
 Ile Gly Gly Val Phe Thr Ser Met Gly Lys Leu Val His Gln Val Phe
 705 710 715 720
 Gly Thr Ala Tyr Gly Val Leu Phe Ser Gly Val Ser Trp Thr Met Lys
 725 730 735
 Ile Gly Ile Gly Ile Leu Leu Thr Trp Leu Gly Leu Asn Ser Arg Asn
 740 745 750
 Thr Ser Leu Ser Met Met Cys Ile Ala Ala Gly Ile Val Thr Leu Tyr
 755 760 765

335

Leu Gly Val Met Val Gln Ala Asp Ser Gly Cys Val Val Ser Trp Lys	770	775	780	
Asn Lys Glu Leu Lys Cys Gly Ser Gly Ile Phe Ile Thr Asp Asn Val	785	790	795	800
His Thr Trp Thr Glu Gln Tyr Lys Phe Gln Pro Glu Ser Pro Ser Lys	805	810	815	
Leu Ala Ser Ala Ile Gln Lys Ala His Glu Glu Asp Ile Cys Gly Ile	820	825	830	
Arg Ser Val Thr Arg Leu Glu Asn Leu Met Trp Lys Gln Ile Thr Pro	835	840	845	
Glu Leu Asn His Ile Leu Ser Glu Asn Glu Val Lys Leu Thr Ile Met	850	855	860	
Thr Gly Asp Ile Lys Gly Ile Met Gln Ala Gly Lys Arg Ser Leu Arg	865	870	875	880
Pro Gln Pro Thr Glu Leu Lys Tyr Ser Trp Lys Thr Trp Gly Lys Ala	885	890	895	
Lys Met Leu Ser Thr Glu Ser His Asn Gln Thr Phe Leu Ile Asp Gly	900	905	910	
Pro Glu Thr Ala Glu Cys Pro Asn Thr Asn Arg Ala Trp Asn Ser Leu	915	920	925	
Glu Val Glu Asp Tyr Gly Phe Gly Val Phe Thr Thr Asn Ile Trp Leu	930	935	940	
Lys Leu Lys Glu Lys Gln Asp Val Phe Cys Asp Ser Lys Leu Met Ser	945	950	955	960
Ala Ala Ile Lys Asp Asn Arg Ala Val His Ala Asp Met Gly Tyr Trp	965	970	975	
Ile Glu Ser Ala Leu Asn Asp Thr Trp Lys Ile Glu Lys Ala Ser Phe	980	985	990	
Ile Glu Val Lys Asn Cys His Trp Pro Lys Ser His Thr Leu Trp Ser	995	1000	1005	
Asn Gly Val Leu Glu Ser Glu Met Ile Ile Pro Lys Asn Leu Ala Gly	1010	1015	1020	
Pro Val Ser Gln His Asn Tyr Arg Pro Gly Tyr His Thr Gln Ile Thr	1025	1030	1035	1040
Gly Pro Trp Trp His Leu Gly Lys Leu Glu Met Asp Phe Asp Phe Cys Asp	1045	1050	1055	
Gly Thr Thr Val Val Val Thr Glu Asp Cys Gly Asn Arg Gly Pro Ser	1060	1065	1070	
Leu Arg Thr Thr Thr Ala Ser Gly Lys Leu Ile Thr Glu Trp Cys Cys	1075	1080	1085	
Arg Ser Cys Thr Leu Pro Pro Leu Arg Tyr Arg Gly Glu Asp Gly Cys	1090	1095	1100	
Trp Tyr Gly Met Glu Ile Arg Pro Leu Lys Glu Lys Glu Glu Asn Leu	1105	1110	1115	1120
Val Asn Ser Leu Val Thr Ala Gly His Gly Gln Val Asp Asn Phe Ser	1125	1130	1135	
Leu Gly Val Leu Gly Met Ala Leu Phe Leu Glu Glu Met Leu Arg Thr	1140	1145	1150	
Arg Val Gly Thr Lys His Ala Ile Leu Leu Val Ala Val Ser Phe Val	1155	1160	1165	
Thr Leu Ile Thr Gly Asn Met Ser Phe Arg Asp Leu Gly Arg Val Met	1170	1175	1180	
Val Met Val Gly Ala Thr Met Thr Asp Asp Ile Gly Met Gly Val Thr	1185	1190	1195	1200

336

Tyr Leu Ala Leu Leu Ala Ala Phe Lys Val Arg Pro Thr Phe Ala Ala
 1205 1210 1215
 Gly Leu Leu Leu Arg Lys Leu Thr Ser Lys Glu Leu Met Met Thr Thr
 1220 1225 1230
 Ile Gly Ile Val Leu Leu Ser Gln Ser Thr Ile Pro Glu Thr Ile Leu
 1235 1240 1245
 Glu Leu Thr Asp Ala Leu Ala Leu Gly Met Met Val Leu Lys Met Val
 1250 1255 1260
 Arg Asn Met Glu Lys Tyr Gln Leu Ala Val Thr Ile Met Ala Ile Leu
 1265 1270 1275 1280
 Cys Val Pro Asn Ala Val Ile Leu Gln Asn Ala Trp Lys Val Ser Cys
 1285 1290 1295
 Thr Ile Leu Ala Val Val Ser Val Ser Pro Leu Phe Leu Thr Ser Ser
 1300 1305 1310
 Gln Gln Lys Thr Asp Trp Ile Pro Leu Ala Leu Thr Ile Lys Gly Leu
 1315 1320 1325
 Asn Pro Thr Ala Ile Phe Leu Thr Thr Leu Ser Arg Thr Ser Lys Lys
 1330 1335 1340
 Arg Ser Trp Pro Leu Asn Glu Ala Ile Met Ala Val Gly Met Val Ser
 1345 1350 1355 1360
 Ile Leu Ala Ser Ser Leu Leu Lys Asn Asp Ile Pro Met Thr Gly Pro
 1365 1370 1375
 Leu Val Ala Gly Gly Leu Leu Thr Val Cys Tyr Val Leu Thr Gly Arg
 1380 1385 1390
 Ser Ala Asp Leu Glu Leu Glu Arg Ala Ala Asp Val Lys Trp Glu Asp
 1395 1400 1405
 Gln Ala Glu Ile Ser Gly Ser Ser Pro Ile Leu Ser Ile Thr Ile Ser
 1410 1415 1420
 Glu Asp Gly Ser Met Ser Ile Lys Asn Glu Glu Glu Glu Gln Thr Leu
 1425 1430 1435 1440
 Thr Ile Leu Ile Arg Thr Gly Leu Leu Val Ile Ser Gly Leu Phe Pro
 1445 1450 1455
 Val Ser Ile Pro Ile Thr Ala Ala Ala Trp Tyr Leu Trp Glu Val Lys
 1460 1465 1470
 Lys Gln Arg Ala Gly Val Leu Trp Asp Val Pro Ser Pro Pro Met
 1475 1480 1485
 Gly Lys Ala Glu Leu Glu Asp Gly Ala Tyr Arg Ile Lys Gln Lys Gly
 1490 1495 1500
 Ile Leu Gly Tyr Ser Gln Ile Gly Ala Gly Val Tyr Lys Glu Gly Thr
 1505 1510 1515 1520
 Phe His Thr Met Trp His Val Thr Arg Gly Ala Val Leu Met His Lys
 1525 1530 1535
 Gly Lys Arg Ile Glu Pro Ser Trp Ala Asp Val Lys Lys Asp Leu Ile
 1540 1545 1550
 Ser Tyr Gly Gly Gly Trp Lys Leu Glu Gly Glu Trp Lys Glu Gly Glu
 1555 1560 1565
 Glu Val Gln Val Leu Ala Leu Glu Pro Gly Lys Asn Pro Arg Ala Val
 1570 1575 1580
 Gln Thr Lys Pro Gly Leu Phe Lys Thr Asn Ala Gly Thr Ile Gly Ala
 1585 1590 1595 1600
 Val Ser Leu Asp Phe Ser Pro Gly Thr Ser Gly Ser Pro Ile Ile Asp
 1605 1610 1615
 Lys Lys Gly Lys Val Val Gly Leu Tyr Gly Asn Gly Val Val Thr Arg
 1620 1625 1630

337

Ser Gly Ala Tyr Val Ser Ala Ile Ala Gln Thr Glu Lys Ser Ile Glu
 1635 1640 1645
 Asp Asn Pro Glu Ile Glu Asp Asp Ile Phe Arg Lys Arg Arg Leu Thr
 1650 1655 1660
 Ile Met Asp Leu His Pro Gly Ala Gly Lys Thr Lys Arg Tyr Leu Pro
 1665 1670 1675 1680
 Ala Ile Val Arg Glu Ala Ile Lys Arg Gly Leu Arg Thr Leu Ile Leu
 1685 1690 1695
 Ala Pro Thr Arg Val Val Ala Ala Glu Met Glu Glu Ala Leu Arg Gly
 1700 1705 1710
 Leu Pro Ile Arg Tyr Gln Thr Pro Ala Ile Arg Ala Val His Thr Gly
 1715 1720 1725
 Arg Glu Ile Val Asp Leu Met Cys His Ala Thr Phe Thr Met Arg Leu
 1730 1735 1740
 Leu Ser Pro Val Arg Val Pro Asn Tyr Asn Leu Ile Ile Met Asp Glu
 1745 1750 1755 1760
 Ala His Phe Thr Asp Pro Ala Ser Ile Ala Ala Arg Gly Tyr Ile Ser
 1765 1770 1775
 Thr Arg Val Glu Met Gly Glu Ala Ala Gly Ile Phe Met Thr Ala Thr
 1780 1785 1790
 Pro Pro Gly Ser Arg Asp Pro Phe Pro Gln Ser Asn Ala Pro Ile Ile
 1795 1800 1805
 Asp Glu Glu Arg Glu Ile Pro Glu Arg Ser Trp Asn Ser Gly His Glu
 1810 1815 1820
 Trp Val Thr Asp Phe Lys Gly Lys Thr Val Trp Phe Val Pro Ser Ile
 1825 1830 1835 1840
 Lys Ala Gly Asn Asp Ile Ala Ala Cys Leu Arg Lys Asn Gly Lys Lys
 1845 1850 1855
 Val Ile Gln Leu Ser Arg Lys Thr Phe Asp Ser Glu Tyr Val Lys Thr
 1860 1865 1870
 Arg Thr Asn Asp Trp Asp Phe Val Val Thr Thr Asp Ile Ser Glu Met
 1875 1880 1885
 Gly Ala Asn Phe Lys Ala Glu Arg Val Ile Asp Pro Arg Arg Cys Met
 1890 1895 1900
 Lys Pro Val Ile Leu Thr Asp Gly Glu Glu Arg Val Ile Leu Ala Gly
 1905 1910 1915 1920
 Pro Met Pro Val Thr His Ser Ser Ala Ala Gln Arg Arg Gly Arg Ile
 1925 1930 1935
 Gly Arg Asn Pro Lys Asn Glu Asn Asp Gln Tyr Ile Tyr Met Gly Glu
 1940 1945 1950
 Pro Leu Glu Asn Asp Glu Asp Cys Ala His Trp Lys Glu Ala Lys Met
 1955 1960 1965
 Leu Leu Asp Asn Ile Asn Thr Pro Glu Gly Ile Ile Pro Ser Met Phe
 1970 1975 1980
 Glu Pro Glu Arg Glu Lys Val Asp Ala Ile Asp Gly Glu Tyr Arg Leu
 1985 1990 1995 2000
 Arg Gly Glu Ala Arg Lys Thr Phe Val Asp Leu Met Arg Arg Gly Asp
 2005 2010 2015
 Leu Pro Val Trp Leu Ala Tyr Arg Val Ala Ala Glu Gly Ile Asn Tyr
 2020 2025 2030
 Ala Asp Arg Arg Trp Cys Phe Asp Gly Val Lys Asn Asn Gln Ile Leu
 2035 2040 2045
 Glu Glu Asn Val Glu Val Glu Ile Trp Thr Lys Glu Gly Glu Arg Lys
 2050 2055 2060

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Lys Leu Lys Pro Arg Trp Leu Asp Ala Arg Ile Tyr Ser Asp Pro Leu
 2065 2070 2075 2080
 Ala Leu Lys Glu Phe Lys Glu Phe Ala Ala Gly Arg Lys Ser Leu Thr
 2085 2090 2095
 Leu Asn Leu Ile Thr Glu Met Gly Arg Leu Pro Thr Phe Met Thr Gln
 2100 2105 2110
 Lys Ala Arg Asp Ala Leu Asp Asn Leu Ala Val Leu His Thr Ala Glu
 2115 2120 2125
 Ala Gly Gly Arg Ala Tyr Asn His Ala Leu Ser Glu Leu Pro Glu Thr
 2130 2135 2140
 Leu Glu Thr Leu Leu Leu Thr Leu Leu Ala Thr Val Thr Gly Gly
 2145 2150 2155 2160
 Ile Phe Leu Phe Leu Met Ser Ala Arg Gly Ile Gly Lys Met Thr Leu
 2165 2170 2175
 Gly Met Cys Cys Ile Ile Thr Ala Ser Ile Leu Leu Trp Tyr Ala Gln
 2180 2185 2190
 Ile Gln Pro His Trp Ile Ala Ala Ser Ile Ile Leu Glu Phe Phe Leu
 2195 2200 2205
 Ile Val Leu Leu Ile Pro Glu Pro Glu Lys Gln Arg Thr Pro Gln Asp
 2210 2215 2220
 Asn Gln Leu Thr Tyr Val Val Ile Ala Ile Leu Thr Val Val Ala Ala
 2225 2230 2235 2240
 Thr Met Ala Asn Glu Met Gly Phe Leu Glu Lys Thr Lys Lys Asp Leu
 2245 2250 2255
 Gly Leu Gly Ser Ile Ala Thr Gln Gln Pro Glu Ser Asn Ile Leu Asp
 2260 2265 2270
 Ile Asp Leu Arg Pro Ala Ser Ala Trp Thr Leu Tyr Ala Val Ala Thr
 2275 2280 2285
 Thr Phe Val Thr Pro Met Leu Arg His Ser Ile Glu Asn Ser Ser Val
 2290 2295 2300
 Asn Val Ser Leu Thr Ala Ile Ala Asn Gln Ala Thr Val Leu Met Gly
 2305 2310 2315 2320
 Leu Gly Lys Gly Trp Pro Leu Ser Lys Met Asp Ile Gly Val Pro Leu
 2325 2330 2335
 Leu Ala Ile Gly Cys Tyr Ser Gln Val Asn Pro Ile Thr Leu Thr Ala
 2340 2345 2350
 Ala Leu Phe Leu Leu Val Ala His Tyr Ala Ile Ile Gly Pro Gly Leu
 2355 2360 2365
 Gln Ala Lys Ala Thr Arg Glu Ala Gln Lys Arg Ala Ala Ala Gly Ile
 2370 2375 2380
 Met Lys Asn Pro Thr Val Asp Gly Ile Thr Val Ile Asp Leu Asp Pro
 2385 2390 2395 2400
 Ile Pro Tyr Asp Pro Lys Phe Glu Lys Gln Leu Gly Gln Val Met Leu
 2405 2410 2415
 Leu Val Leu Cys Val Thr Gln Val Leu Met Met Arg Thr Thr Trp Ala
 2420 2425 2430
 Leu Cys Glu Ala Leu Thr Leu Ala Thr Gly Pro Ile Ser Thr Leu Trp
 2435 2440 2445
 Glu Gly Asn Pro Gly Arg Phe Trp Asn Thr Thr Ile Ala Val Ser Met
 2450 2455 2460
 Ala Asn Ile Phe Arg Gly Ser Tyr Leu Ala Gly Ala Gly Leu Leu Phe
 2465 2470 2475 2480
 Ser Ile Met Lys Asn Thr Thr Asn Thr Arg Arg Gly Thr Gly Asn Ile
 2485 2490 2495

Gly Glu Thr Leu Gly Glu Lys Trp Lys Ser Arg Leu Asn Ala Leu Gly
 2500 2505 2510
 Lys Ser Glu Phe Gln Ile Tyr Lys Lys Ser Gly Ile Gln Glu Val Asp
 2515 2520 2525
 Arg Thr Leu Ala Lys Glu Gly Ile Lys Arg Gly Glu Thr Asp His His
 2530 2535 2540
 Ala Val Ser Arg Gly Ser Ala Lys Leu Arg Trp Phe Val Glu Arg Asn
 2545 2550 2555 2560
 Met Val Thr Pro Glu Gly Lys Val Val Asp Leu Gly Cys Gly Arg Gly
 2565 2570 2575
 Gly Trp Ser Tyr Tyr Cys Gly Gly Leu Lys Asn Val Arg Glu Val Lys
 2580 2585 2590
 Gly Leu Thr Lys Gly Gly Pro Gly His Glu Glu Pro Ile Pro Met Ser
 2595 2600 2605
 Thr Tyr Gly Trp Asn Leu Val Arg Leu Gln Ser Gly Val Asp Val Phe
 2610 2615 2620
 Phe Ile Pro Pro Glu Lys Cys Asp Thr Leu Leu Cys Asp Ile Gly Glu
 2625 2630 2635 2640
 Ser Ser Pro Asn Pro Thr Val Glu Ala Gly Arg Thr Leu Arg Val Leu
 2645 2650 2655
 Asn Leu Val Glu Asn Trp Leu Asn Asn Asn Thr Gln Phe Cys Ile Lys
 2660 2665 2670
 Val Leu Asn Pro Tyr Met Pro Ser Val Ile Glu Lys Met Glu Ala Leu
 2675 2680 2685
 Gln Arg Lys Tyr Gly Gly Ala Leu Val Arg Asn Pro Leu Ser Arg Asn
 2690 2695 2700
 Ser Thr His Glu Met Tyr Trp Val Ser Asn Ala Ser Gly Asn Ile Val
 2705 2710 2715 2720
 Ser Ser Val Asn Met Ile Ser Arg Met Leu Ile Asn Arg Phe Thr Met
 2725 2730 2735
 Arg Tyr Lys Lys Ala Thr Tyr Glu Pro Asp Val Asp Leu Gly Ser Gly
 2740 2745 2750
 Thr Arg Asn Ile Gly Ile Glu Ser Glu Ile Pro Asn Leu Asp Ile Ile
 2755 2760 2765
 Gly Lys Arg Ile Glu Lys Ile Lys Gln Glu His Glu Thr Ser Trp His
 2770 2775 2780
 Tyr Asp Gln Asp His Pro Tyr Lys Thr Trp Ala Tyr His Gly Ser Tyr
 2785 2790 2795 2800
 Glu Thr Lys Gln Thr Gly Ser Ala Ser Ser Met Val Asn Gly Val Val
 2805 2810 2815
 Arg Leu Leu Thr Lys Pro Trp Asp Val Val Pro Met Val Thr Gln Met
 2820 2825 2830
 Ala Met Thr Asp Thr Thr Pro Phe Gly Gln Gln Arg Val Phe Lys Glu
 2835 2840 2845
 Lys Val Asp Thr Arg Thr Gln Glu Pro Lys Glu Gly Thr Lys Lys Leu
 2850 2855 2860
 Met Lys Ile Thr Ala Glu Trp Leu Trp Lys Glu Leu Gly Lys Lys Lys
 2865 2870 2875 2880
 Thr Pro Arg Met Cys Thr Arg Glu Glu Phe Thr Arg Lys Val Arg Ser
 2885 2890 2895
 Asn Ala Ala Leu Gly Ala Ile Phe Thr Asp Glu Asn Lys Trp Lys Ser
 2900 2905 2910
 Ala Arg Glu Ala Val Glu Asp Ser Arg Phe Trp Glu Leu Val Asp Lys
 2915 2920 2925

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Glu Arg Asn Leu His Leu Glu Gly Lys Cys Glu Thr Cys Val Tyr Asn
 2930 2935 2940
 Met Met Gly Lys Arg Glu Lys Lys Leu Gly Glu Phe Gly Lys Ala Lys
 2945 2950 2955 2960
 Gly Ser Arg Ala Ile Trp Tyr Met Trp Leu Gly Ala Arg Phe Leu Glu
 2965 2970 2975
 Phe Glu Ala Leu Gly Phe Leu Asn Glu Asp His Trp Phe Ser Arg Glu
 2980 2985 2990
 Asn Ser Leu Ser Gly Val Glu Gly Glu Gly Leu His Lys Leu Gly Tyr
 2995 3000 3005
 Ile Leu Arg Asp Val Ser Lys Lys Glu Gly Gly Ala Met Tyr Ala Asp
 3010 3015 3020
 Asp Thr Ala Gly Trp Asp Thr Arg Ile Thr Leu Glu Asp Leu Lys Asn
 3025 3030 3035 3040
 Glu Glu Met Val Thr Asn His Met Glu Gly Glu His Lys Lys Leu Ala
 3045 3050 3055
 Glu Ala Ile Phe Lys Leu Thr Tyr Gln Asn Lys Val Val Arg Val Gln
 3060 3065 3070
 Arg Pro Thr Pro Arg Gly Thr Val Met Asp Ile Ile Ser Arg Arg Asp
 3075 3080 3085
 Gln Arg Gly Ser Gly Gln Val Gly Thr Tyr Gly Leu Asn Thr Phe Thr
 3090 3095 3100
 Asn Met Glu Ala Gln Leu Ile Arg Gln Met Glu Gly Glu Gly Val Phe
 3105 3110 3115 3120
 Lys Ser Ile Gln His Leu Thr Ile Thr Glu Glu Ile Ala Val Gln Asn
 3125 3130 3135
 Trp Leu Ala Arg Val Gly Arg Glu Arg Leu Ser Arg Met Ala Ile Ser
 3140 3145 3150
 Gly Asp Asp Cys Val Val Lys Pro Leu Asp Asp Arg Phe Ala Ser Ala
 3155 3160 3165
 Leu Thr Ala Leu Asn Asp Met Gly Lys Ile Arg Lys Asp Ile Gln Gln
 3170 3175 3180
 Trp Glu Pro Ser Arg Gly Trp Asn Asp Trp Thr Gln Val Pro Phe Cys
 3185 3190 3195 3200
 Ser His His Phe His Glu Leu Ile Met Lys Asp Gly Arg Val Leu Val
 3205 3210 3215
 Val Pro Cys Arg Asn Gln Asp Glu Leu Ile Gly Arg Ala Arg Ile Ser
 3220 3225 3230
 Gln Gly Ala Gly Trp Ser Leu Arg Glu Thr Ala Cys Leu Gly Lys Ser
 3235 3240 3245
 Tyr Ala Gln Met Trp Ser Leu Met Tyr Phe His Arg Arg Asp Leu Arg
 3250 3255 3260
 Leu Ala Ala Asn Ala Ile Cys Ser Ala Val Pro Ser His Trp Val Pro
 3265 3270 3275 3280
 Thr Ser Arg Thr Thr Trp Ser Ile His Ala Lys His Glu Trp Met Thr
 3285 3290 3295
 Thr Glu Asp Met Leu Thr Val Trp Asn Arg Val Trp Ile Gln Glu Asn
 3300 3305 3310
 Pro Trp Met Glu Asp Lys Thr Pro Val Glu Ser Trp Glu Glu Ile Pro
 3315 3320 3325
 Tyr Leu Gly Lys Arg Glu Asp Gln Trp Cys Gly Ser Leu Ile Gly Leu
 3330 3335 3340
 Thr Ser Arg Ala Thr Trp Ala Lys Asn Ile Gln Ala Ala Ile Asn Gln
 3345 3350 3355 3360

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Val	Arg	Ser	Leu	Ile	Gly	Asn	Glu	Glu	Tyr	Thr	Asp	Tyr	Met	Pro	Ser
					3365				3370					3375	
Met	Lys	Arg	Phe	Arg	Arg	Glu	Glu	Glu	Glu	Ala	Gly	Val	Leu	Trp	
			3380					3385					3390		

<210> 29
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 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:/Note =
 synthetic construct

<400> 29
 cuacgu 6

<210> 30
 <211> 6
 <212> RNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:/Note =
 synthetic construct

<400> 30
 acguag 6

<210> 31
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 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:/Note =
 synthetic construct

<400> 31
 tagagagcag atctctg 17

<210> 32
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<220>
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 synthetic construct

<400> 32
 tgtgaccatg ccggtgcga tgcactcacc ga 32

342

<210> 33
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:/Note =
synthetic construct

<400> 33
tgctggccac ttaactacgc gtgatggaga gccgcgca 38

<210> 34
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<212> DNA
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<220>
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synthetic construct

<400> 34
tgtaatgatg ccggccgcga tgcataaaaa tga 33

<210> 35
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<220>
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<400> 35
ggcgtttcac ttgtcaacgc gtgatggcga acccctca 38

<210> 36
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<400> 36
agtgattccg ccggcagcta tgcacgtcat agccat 36

<210> 37
<211> 39
<212> DNA
<213> Artificial Sequence

343

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<400> 37

ggagcagtta ccctctctac gcgtcaaggg aaggtgatg

39

<210> 38

<211> 44

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence:/Note =
synthetic construct

<400> 38

gaagagcaga actccgccgg ctgcgagaaa cgtgagagct atgg

44

<210> 39

<211> 28

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<400> 39

Ser Ala Gly Met Ile Ile Met Leu Ile Pro Thr Val Met Ala Phe His

1

5

10

15

Leu Thr Thr Arg Gln Gly Lys Val Met Met Thr Val

20

25

<210> 40

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

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synthetic construct

<400> 40

Gln Gly Lys Val Met Met Thr Val

1

5

<210> 41

<211> 56

<212> DNA

<213> Artificial Sequence

344

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<400> 41

aattcaacgc gtacatccgc gggcaccgga attgcagtca tgattggcct gatggc 56

<210> 42

<211> 32

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<400> 42

Ser Ala Gly Thr Gly Ile Ala Val Met Ile Gly Leu Ile Ala Ser Val

1	5	10	15
Gly Ala Val Thr Leu Ser Asn Phe Gln Gly Lys Val Met Met Thr Val			
20	25	30	

<210> 43

<211> 29

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:/Note =
synthetic construct

<400> 43

Thr Gly Ile Ala Val Met Ile Gly Leu Ile Ala Ser Val Gly Ala Val

1	5	10	15
Thr Leu Ser Asn Phe Gln Gly Lys Val Met Met Thr Val			
20	25		

<210> 44

<211> 26

<212> DNA

<213> Artificial Sequence

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<223> synthetic construct

<400> 44

ttcatattga gctatctttc cttcta 26

<210> 45

<211> 20

<212> DNA
<213> Artificial Sequence

<220>
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<400> 45
gtgtgccaaag tttaagtggtg 20

<210> 46
<211> 19
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<400> 46
tggacgggtga ctatcactg 19

<210> 47
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<212> DNA
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<220>
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<400> 47
aagccatgat ttctttttca ttgtca 26

<210> 48
<211> 20
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<220>
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<400> 48
cagggctaga ttttaacgag 20

<210> 49
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<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 49
agtggtaagt ctagaaacca c 21

<210> 50
<211> 24

<212> DNA
<213> Artificial Sequence

<220>
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<400> 50
tccacaaaca gtggtttcta gact 24

<210> 51
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<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 51
tggtgctgac aatgaaaaag aa 22

<210> 52
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<212> DNA
<213> Artificial Sequence

<220>
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<213> Artificial Sequence

<220>
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<400> 53
tggggatgtta aagccccaga ggt 23

<210> 54
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<212> DNA
<213> Artificial Sequence

<220>
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<400> 54
tcatggcttg tccacaaaca g 21

<210> 55
<211> 21

347

<212> DNA
<213> Artificial Sequence

<220>
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<400> 55
ccagtaaato ttgtctgttc c 21

<210> 56
<211> 23
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<220>
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<400> 56
cgtcccttgc ggtgatgtgc atc 23

<210> 57
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
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<400> 57
attctgctga catggctagg 20

<210> 58
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 58
tcctaggtac agtgtgacc 19

<210> 59
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 59
agattccact aacgtctccc acg 23

<210> 60
<211> 21

348

<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 60
aattgaacca catcctactt g 21

<210> 61
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 61
ttgtgttcca tgggttgtag 20

<210> 62
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
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<400> 62
tatgatttta gcttttcccc agctt 25

<210> 63
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
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<400> 63
gccacaaccc atggaacac 19

<210> 64
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
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<400> 64
atgaaggtgg tgttctgtac 20

<210> 65
<211> 24

<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 65
tcctaaacac cttgtcctca atct 24

<210> 66
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 66
gctaaggcat cacaagaagg 20

<210> 67
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 67
cgatccctgga tgtaggtcc 19

<210> 68
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 68
cagccctctt tgagccggag a 21

<210> 69
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic construct

<400> 69
aatataaaca caccagaagg 20

<210> 70
<211> 19

<212> DNA
<213> Artificial Sequence

<220>
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<400> 70
tccccgtcta tagctgcac 19

<210> 71
<211> 25
<212> DNA
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<220>
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<400> 71
tgtcaatatc acgaataaca gacct 25

<210> 72
<211> 19
<212> DNA
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<220>
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<400> 72
cacaggacaa ccagctagc 19

<210> 73
<211> 19
<212> DNA
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<220>
<223> synthetic construct

<400> 73
aataatccca tctcattgg 19

<210> 74
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<212> DNA
<213> Artificial Sequence

<220>
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<400> 74
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(19) World Intellectual Property Organization
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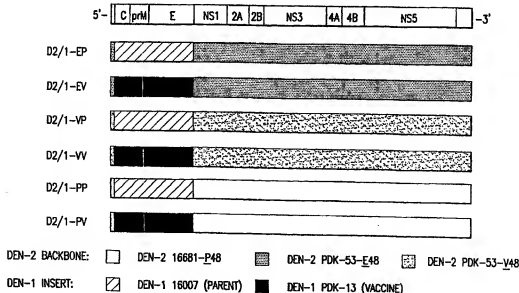
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- (71) Applicant (for all designated States except US): THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Centers for Disease Control and Prevention, Technology Transfer Office, 1600 Clifton Road, N.E., M/S E-67, Atlanta, GA 30333 (US).
- (72) Inventors; and
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- (74) Agents: MILLER, Mary, L. et al.; Needle & Rosenberg, P.C., Suite 1200, 127 Peachtree Street, N.E., Atlanta, GA 30303-1811 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

[Continued on next page]

(54) Title: AVIRULENT, IMMUNOGENIC FLAVIVIRUS CHIMERAS



(57) Abstract: Chimeric flaviviruses that are avirulent and immunogenic are provided. The chimeric viruses are constructed to contain amino acid mutations in the nonstructural proteins of a flavivirus. Chimeric viruses containing the attenuation-mutated nonstructural genes of the virus are used as a backbone into which the structural protein genes of a second flavivirus strain are inserted. These chimeric viruses elicit pronounced immunogenicity yet lack the accompanying clinical symptoms of viral disease. The attenuated chimeric viruses are effective as immunogens or vaccines and may be combined in a pharmaceutical composition to confer simultaneous immunity against several strains of pathogenic flaviviruses.

WO 01/60847 A3



(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(88) Date of publication of the international search report:
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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 01/05142

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/40 C12N7/01 C07K14/18 A61K39/12 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	ISSN: 0042-6822 the whole document	3-14, 16-39, 44-59

-/-

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *Z* document member of the same patent family

Date of the actual completion of the international search

6 August 2001

Date of mailing of the international search report

21/08/2001

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Mandl, B

INTERNATIONAL SEARCH REPORT

No. of Application No
PCT/US 01/05142

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 06214 A (US HEALTH) 1 April 1993 (1993-04-01)	1
Y	page 7, line 15 - line 21 page 15, line 12 - line 17 page 16, line 12 - line 19 ---	3-14, 16-39, 44-59
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PCT/US 01/05142

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